UNIVERSITY OF VIRGINIA

IRB-HSR Research Guidance

Version Date: October 3, 2012

PREFACE

The IRB-HSR Research Guidance is a guide for those involved in human subject research through the University of Virginia. This guidance details the elements of the research protocol, particular issues that study team members should consider in conducting different types of research, and the required elements and documentation of the informed consent process. The guide is based on the IRB-HSR Standard Operating Procedures, applicable federal regulations, Virginia state statutes, and University of Virginia policy as they pertain to the conduct of human research at the University of Virginia.

Since the field of human subject protection is constantly evolving, sections of the guide may be subject to change.

INTRODUCTION

In order to ensure the rights, welfare, and protection of all subjects, all human subjects' research, and all other activities, which in part involve human subject research, regardless of sponsorship, must be reviewed and approved by the IRB prior to initiation. This includes all interventions and interactions with human subjects for research, including advertising, recruitment and/or screening of potential subjects.

Human subject's research is any research or clinical investigation that involves human subjects.

> For more information regarding the types of projects that include research with human subjects see Examples of Activities That Do and Do Not Require IRB–HSR Review

WHICH IRB SHOULD I SUBMIT TO?

There are two IRB's at the University of Virginia. The IRB for Health Sciences Research (IRB-HSR) and the IRB for Social and Behavioral Research (SBS). If you are not sure which IRB you should submit too, please review the IRB Determination Algorithm.

If you still not certain which IRB to submit too after reviewing this information, please contact the Director of either IRB to discuss your study.

ALTERNATIVE IRB OF RECORD

Researchers wishing to open Phase 3 adult or pediatric cooperative group oncology trials that have been approved by the National Cancer Institute Central Institutional Review Board (NCI CIRB) or the NCI Pediatric Central IRB (Pediatric CIRB) may submit the appropriate paperwork to the IRB-HSR. If the IRB-HSR accepts the NCI CIRB/Pediatric CIRB review, the NCI CIRB/Pediatric CIRB will become the IRB of record.

Researchers wishing to open an expanded access protocol or a Phase 1 or 2 adult cooperative group oncology trials or Phase 3 trials which cannot be opened through the CIRB or a pediatric cooperative group oncology trial may use the Western Institutional Review Board (WIRB) as the IRB of record for the trial. The PI will submit the appropriate paperwork to WIRB and the IRB-HSR.

Researchers wishing to open an expanded access protocol may use a central IRB as the IRB of record for the trial. The PI will submit the appropriate paperwork to the central IRB and the IRB-HSR.

HUMAN RESEARCH ACTIVITIES PERFORMED AT OTHER INSTITUTIONS

BACKGROUND

All research activities performed by, or under the direction of, UVa personnel or which use University resources, must comply with applicable UVa policies and procedures, regardless of funding and whether performed in UVa facilities or at offsite locations.

REQUIREMENTS FOR APPROVAL OF RESEARCH AT NON-UVA FACILITIES

Any human subjects research conducted in whole or in part outside of UVa facilities must be reviewed and approved by the UVa IRB prior to initiation if it satisfies any of the following criteria unless an IRB Authorization Agreement is in place naming the outside IRB as the IRB of record.

1. It is conducted by or under the direction of UVa personnel in connection with his or her UVa responsibilities.
2. It uses UVa property, facilities, or resources to support or carry out the research.
3. The name of the University of Virginia is used in applying for funds (intra or extramural).
4. The name of the University of Virginia is used in explanations and/or representations to subjects.
5. The investigator plans to use his/her University of Virginia association in any publication or public presentation resulting from the research.
6. Non-public information from UVa will be used to identify or contact human research subjects or prospective subjects.

IRB APPROVAL OF RESEARCH AT A NON- UVA INSTITUTION

The researcher will need to obtain approval from the Non-UVa IRB in addition to the UVa IRB for any research done at a Non- UVa Institution unless an IRB Authorization Agreement is in place naming an outside IRB as the IRB of record. Procedures may be found on the IRB-HSR website at IRB Authorization Agreements.

MANAGEMENT OF THE IRB-HSR

IRB-HSR CONTACTS

The IRB-HSR staff is willing to answer any questions regarding the participation of human subjects in research or the review of applications by the IRB. Any questions regarding IRB review or the content of this guide should be directed to the Associate Vice President for Research (AVPR) or one of the IRB chairs or Directors.

IRB-HSR Administrative Staff

The IRB-HSR Administrative Staffs is a unit within the Office of the Vice President for Research and report directly to the Associate Vice President for Research. The IRB-HSR Administrative Staff:

- Assists in preparing the agenda for and monitoring IRB-HSR meetings;
- Maintains files on all human subjects research (including copies of relevant correspondence between the IRB-HSR and investigators) that takes place at the University of Virginia;
- Maintains databases for tracking studies;
- Prepare and maintain meeting minutes;
- Screens research applications for completeness prior to initiating the IRB-HSR review process;
- Acts as a resource for investigators on general regulatory information, guidance with forms, and assistance in preparing an application for IRB-HSR review;
- Maintains the institution's IRB-HSR membership rosters for the FWA ;
- Provides staff support to the IRB-HSRs for all written correspondence;
- Sends notices of approval, study closure (other than closure of the study by the investigator), and termination;
- Generates and sends reminder notices to investigators of upcoming continuing reviews;
- Maintains information on federal regulations relating to human subjects research;
- Provides education regarding the IRB-HSR process and regulations to the University community;
- Provides education opportunities to IRB-HSR members;
- Maintains records of IRB-HSR membership including training;
- Conducts quality assurance and quality improvement for the IRB-HSR

IRB-HSR Website

Information from the IRB-HSR may also be found on the UVa IRB-HSR Website

EDUCATION

REQUIRED EDUCATION

The University of Virginia requires every investigator / key personnel to complete an online course on human subject protections. Key personnel include anyone who will have access to subjects or identifiable data during the course of the study (e.g.) Principal Investigator, Sub-investigators, Research Coordinators.

The CITI Program satisfies UVA's IRB online training requirement for investigators involved in human subject research. At UVA, investigators involved in human subject research are required to take online training once every three years. Required Training CITI Program

VOLUNTARY EDUCATION

Educational Activities Aimed at UVa Researchers

The IRB-HSR schedules and advertises educational workshops throughout the calendar year directed at investigators and their research associates. These workshops cover topics that include University of Virginia policies and procedures as well as federal regulatory requirements.

Members of the IRB-HSR or IRB-HSR staff may present information at meetings in academic departments or give lectures in University classes, to emphasize selected aspects of human subject research, and to keep various constituencies abreast of activities of the IRB-HSR.

In Person Education
Learning Shots-IRB Online Education

Educational Activities Aimed at the Community at Large

The VPR Office has developed a website for potential subjects aimed at the general population in Virginia and the surrounding communities explaining research. The website lists a number of questions a potential subject may wish to ask if approached to be a subject in a study.

The IRB-HSR maintains an internet website that contains detailed information on the University of Virginia human subjects review process as well as links to federal regulations and regulatory agencies, the OHRP Institutional Review Board Guidebook, the Belmont Report, and other guidance documents.

The IRB-HSR also maintains a small library of materials that include books and videotapes discussing ethical and regulatory issues relating to human subjects research. These materials are available upon request to the entire UVa community.

Educational Activities Aimed at Members of the IRB-HSR

At the time of induction of a new member, members of the professional staff from the IRB-HSR review with the member procedures of the IRB-HSR and the general regulatory framework from which procedures and policies are derived.

Information offered by the IRB-HSR includes the University of Virginia human subject's website containing detailed information on the University of Virginia human subjects review process as well as links to federal regulations, the OHRP Institutional Review Board (IRB-HSR) Guidebook, the Belmont Report, and other guidance documents.

On an ongoing basis, members will receive information about educational opportunities that are available.

Educational Activities Aimed at Members of the University Administration

The University of Virginia provides the opportunity for professional staff members from the Office of the Associate Vice President for Research and Graduate Studies to attend, at least annually, conferences or workshops on human subject issues in research. Upon return, these individuals brief appropriate members of the University community on relevant information obtained.

INSPECTIONS BY OUTSIDE AGENCIES: INVESTIGATOR GUIDANCE FOR FDA INSPECTIONS

INTRODUCTION

The Food and Drug Administration (FDA) Bioresearch Monitoring Program (BIMO) oversees FDA-regulated research by performing site visits to clinical investigators, sponsors, Institutional Review Boards (IRBs) and non-clinical animal laboratories. Site visits help to assure that human subjects and animals are protected from undue hazards and to verify that research data supporting new human and animal product approvals are reliable. FDA conducts inspections to determine if investigators are in compliance with FDA regulations. Inspections can be announced or unannounced. Most inspections are routinely performed to verify data submitted to FDA (e.g., at sites enrolling the largest number of subjects), but can also occur as a result of a complaint made to FDA, due to sponsor concerns, as a result of a review division request within FDA, or based upon current and ongoing public health issues.

PREPARING FOR AN INSPECTION

Investigators should take the following actions when notified that an on-site inspection by FDA is going to occur:

- Determine the nature (i.e., "for cause," routine, etc.) and the scope of the audit. What protocols will be reviewed? How long will the FDA inspector(s) be on-site?
- Routine inspections are generally scheduled within ten (10) working days of the initial contact and cannot be postponed without sufficient justification.
- Inform the following groups (as applicable) when initially contacted by FDA so that each party can prepare for the visit, as necessary:
    - Research team and ancillary support services (e.g., pharmacy etc.)
    - School of Medicine Clinical Trials Office (SOM CTO)
    - Department Chair
    - IRB-HSR
- Schedule an appropriate room for the auditors. Provide the FDA inspector(s) with office supplies, access to a copier and fax machine, and a list of staff contact names and telephone/pager numbers.
- Pre-review all research records (medical and regulatory), and make them available to the inspector(s) at the time of the site visit. Investigators must allow the FDA to access, copy and verify any case history and/or drug or device administration records made by the research team or others.
- At the conclusion of the site visit, the FDA inspector conducts an exit interview with the principal investigator and associated research team members. A written "Notice of Inspection" (Form FDA 483) is typically generated if deficiencies are found.

- Forward a copy of post-audit communications and/or FDA Form 483 to the research team, Department Chair, IRB-HSR and the School of Medicine Clinical Trials Office. Consult with SOMCTO staff for assistance in responding to audit findings.

For more information about FDA site inspections, consult the complete FDA Compliance Program Guidance Manual.

MONITORING

POST APPROVAL MONITORING ACTIVITIES

The Post Approval Monitoring and Education program has three goals:

- Enhance protection of research subjects
- Enhance quality of research data
- Enhancement of the education program

Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures.

The VPR Post Approval Monitor(s) may attend IRB meetings to provide feedback to the IRB members.

The reason(s) for on-site review may include:

- random selections,
- complex projects involving unusual levels or types of risks to subjects,
- projects conducted by an investigator who previously failed to comply with IRB determinations, or
- projects where continuing review or reports from other sources have indicated that changes without IRB approval may have occurred or subjects were consented inappropriately,
- HIPAA non-compliance,
- subject or whistleblower complaints, or
- Request by an IRB member and with approval by the IRB.

Full reports will be submitted to the IRB post approval monitoring sub-committee on a monthly basis. Aggregate summaries of the reports will be submitted to the full membership of the IRB on a quarterly basis. Information from the reports will also be reviewed by staff of the IRB the IRB Education Coordinator and the School of Medicine Clinical Trials

POST APPROVAL MONITORING PROCESS

The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or
- observation of the consent process and/or research procedures.

Examples of when observation of the consent process could occur are:

- Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
- IRB is made aware of a complaint or concern with regard to the informed consent process; or
- IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

Post Approval Monitoring Working Group

The Research Compliance Monitors submit reports to a Post Approval Monitoring (PAM) Working Group consisting of the Associate VP for Research, Research Compliance Coordinators, IRB Directors, IRB Educators, and professional staff of the office of the School of Medicine Clinical Trials office. The PAM Working Group will review the reports and make recommendations to the IRB PAM Advisory Committee.

IRB Post Approval Monitoring Advisory Committee

The IRB post-approval monitoring advisory committee (PAM Committee) will include no more than 6 members and will be chaired by the IRB chair. The members will serve on the PAM Committee for a two year term.

The reports and the recommendations from the PAM Working Group will be presented to the PAM Committee on a monthly basis. All documents will be given to the members prior to the meeting to allow them time to review the reports.

Aggregate summaries of the reports will be submitted to the full membership of the IRB on a quarterly basis. Information from the reports will also be reviewed by staff of the IRB, the IRB Education Coordinator and the School of Medicine Clinical Trials Office for purposes of education updates.

The IRB Post Approval Monitoring Advisory Committee may consult with outside specialists as deemed necessary. The IRB Chair will then pick a primary reviewer to present the information and recommended actions to the full IRB.

Any of the following may occur as a result of a monitoring report:

Possible actions the IRB may take include:

- Recommendation to implement corrective actions
- Request the post approval monitors review all active protocols of Principal Investigator
- Request subsequent post-approval monitoring visits
- Investigators to attend educational seminar
- Suspension of subject enrollment
- Suspension (protocol closed to treatment)
- Termination of IRB-HSR approval (protocol closed)
- Require protocol to be re-audited at specific time/ enrollment period
- Require PI to be mentored for a specific period of time

- Replacement of PI
- Disallow PI to conduct research for a period of time
- Require PI to notify subjects of non-compliance and get their permission to use the data
- Notification of chair, dean, and research ethics committee
- Require PI to inform journals of noncompliance when submitting for publication
- Reporting of non-Compliance to federal agencies (required if suspension or termination occurred)
- Notification of all investigators at institution via education programs to ensure all are aware of regulations, so the noncompliance would be less likely to happen again.
- If noncompliance put subjects at risk, may request a "peer review"
- Consult with OHRP regarding appropriate corrective action

If there are concerns regarding scientific misconduct such as fraud or IRS issues, notify the UVA Research Integrity Officer at 434-924-3606.

The monitoring report is reviewed at a convened meeting of the IRB.

When accepted by the IRB, the report findings and committee recommendations are forwarded to the principal investigator for response and resolution of any outstanding issues, the AVPR, and others, including federal regulatory agencies, as deemed necessary by the IRB. A written record of auditing activities is maintained in the study file and in the AVPR office.

NON-COMPLIANCE: AUDITING FOR CAUSE

Information regarding non-compliance in human subject's studies may come to the attention of the IRB in several ways.

These include:

- information contained in new applications,
- continuing reviews,
- adverse event reports, and
- reports from collaborators, employees, the public, or subjects.

The chair of the appropriate IRB reviews allegations of non-compliance.

The chair makes a determination as to whether the alleged practices appear to

- cause injury or any other unanticipated problems involving risks to subjects or others, or
- constitute serious or continuing non-compliance with IRB determinations or federal regulations.

In such cases, the chair may suspend the study procedures pending a timely investigation and review by the full IRB.

At the discretion of the chair or board, a study may continue while minor incidents of noncompliance are under investigation. The chair may elect to discuss an allegation of noncompliance with the IRB prior to suspending the protocol if it is apparent that there is no increased risk to subjects.

The Chair and/or the AVPR, may suspend studies when:

- the violation is a clear violation of the regulations,

- a violation of university policy, or
- there is imminent danger to subjects.

The chair and/or the IRB will be notified of this action as soon as possible.

Allegations of Misconduct

Investigations by the IRB focus on the protection of study subjects. In cases that involve allegations of research misconduct, the chair contacts the University of Virginia Research Integrity Officer (RIO) for further action. This does not preclude the chair or any member of the IRB from independently contacting the RIO about any allegation of research misconduct. Inquiries or investigations into research misconduct do not preclude IRB review and actions.

The following are the recommended procedures for resolving alleged non-compliance:

- When made aware of a potential problem, AVPR staff compiles file information and presents concerns to the appropriate IRB chair.
- The chair makes a determination to refer the matter to the Post Approval Monitor to contact the principal investigator. The purpose of such contact is fact-finding, i.e., to determine whether the problem is intentional, unintentional and/or the result of mistake or oversight.
- The chair may temporarily halt enrollment and/or data collection until full board review occurs (with consideration of effect in therapeutic trials). However, if the chair has determined there is no increased risk to the subjects; the study may continue and no corrective action will be required by the researchers until the audit is accepted by the IRB.
- The IRB Director or designee documents the outcome of any and all communications and discussions in writing, by either e-mail or paper memo with a copy to the IRB files. Such documentation should be factual and objective.
- When the initial inquiry does not result in resolution of the matter, a meeting with the principal investigator is scheduled as soon as possible. A member of the IRB staff documents results of the meeting.
- Any discussions, findings, efforts to achieve resolution and sanction recommendations are documented at the next IRB meeting by the chair or IRB Research Compliance Monitor. The IRB is granted authority to recommend sanctions to the Research Compliance Monitor.
- At a convened meeting, a quorum of IRB members will discuss the findings, recommend actions, and vote to approve the recommended actions.
- The IRB has the authority to suspend or terminate IRB approval of protocols that are found to be non-compliant with institutional policies and procedures, state statutes, and/or federal laws or regulations.
- The AVPR sends written notification of actions taken to the principal investigator with copies to the departmental chair, AVPR and the research offices of other affiliated institutions, as determined by the IRB. To the extent that any action includes suspension or termination, in cases of externally funded programs, notice will be sent to the Office of Sponsored Programs or the SOM Grants and Contracts Office. Federal regulatory agencies are notified of actions as required by federal regulation.

IRB-HSR RECORD REQUIREMENTS

IRB-HSR Membership Roster

A current (and previous) roster of IRB-HSR members and their areas of expertise may be found on the IRB-HSR website. The roster is updated as board membership changes.

Meeting Minutes

Members and alternates of the IRB-HSR receive minutes of full board meetings. Minutes include written notification of all new projects approved (full board and expedited), projects determined to be exempt, continuing reviews (full board and expedited), modifications (full board and expedited), and reportable adverse experience.

Minutes are generated that record the following information:

- attendance at each meeting including names of voting and non-voting members or attendees;
- actions taken by the board including initial and continuing review of research;
- the vote on actions taken including the number for, against, and names of those abstaining and absent
- notation when a member declares a conflict to interest
- the basis for requiring changes in or disapproving research;
- a written summary of the discussion of controverted issues and their resolution;
- specific comments relevant to inclusion/exclusion of certain populations;
- amendments or modifications that require full board review;
- documentation and review reports of adverse reactions reports;
- in addition to the review of pending applications, meeting minutes may include information regarding modifications, expirations, emergency/single patient use, adverse experiences, and any other business appropriate for board meetings.

DHHS regulations at 45 CFR 46.116(d) require that the IRB-HSR make and document their actions when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent.

Similarly, DHHS regulations require specific findings noted in the minutes such as:

- approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR46.117(c)];
- approving research involving pregnant women, human fetuses, or neonates (see 45CFR 46.204-207);
- approving research involving prisoners (see 45 CFR 46.305-306); or
- approving research involving children (see 45 CFR 46.404-407), the IRB-HSR should document such findings.

Record Retention by the IRB-HSR

The IRB-HSR maintains file copies of all research proposals reviewed. This file includes all documentation relevant to a protocol including but not limited to the protocol, consent form(s) (if applicable) , assent (if applicable) modifications, adverse event or unexpected problem reports, status forms, approvals, protocol violation or exception reports, and any written communication regarding the protocol. The IRB-HSR files will also retain all grant applications reviewed by the IRB-HSR, along with the reviewer's form, and approval forms. In addition the IRB-HSR will maintain documentation of exempt applications, emergency use reports, "not engaged" or "coded research" applications. Other documents in the IRB-HSR include minutes, standard operating procedures, administrative guidance, research guidance, member guidance and any other correspondence pertaining to IRB-HSR operations.

Paper or electronic records on human subjects research are maintained by the IRB-HSR for a minimum of three years after notice of study closure and records relating to research which is conducted shall be retained for at least three years after the completion of the research (45 CFR 46.115, 21 CFR 56.115). If the protocol involved a waiver of consent or data use agreement under HIPAA regulations, the files will be kept for a minimum of six years after notice of study closure.

The IRB-HSR maintains a permanent record of all closed files on IRB-HSR Online (studies closed since January, 2000). Researchers are encouraged to communicate with the sponsor or the School of Medicine Clinical Trials Office to determine how long they should retain documents.

LEVELS OF REVIEW

Activities that constitute human subject research are determined by the University of Virginia IRBs. The IRBs delegate this decision to the IRB chair, vice chair, experienced member designee or experienced IRB staff. The decision by the chair, vice chair, experienced member designee or experienced IRB staff is based on whether the activity:

- represents “research,” and involves “humans” as participants, (as defined in 45 CFR 46.102(d), 45 CFR 46.102(f) and
- *if the study does not fall under FDA regulations*: “engages” the University of Virginia (as defined in the OHRP guidance document “Engagement of Institutions in Research” respectively), or meets the definition of Coded Research (as defined in the OHRP guidance document "Research Involving Coded Private Information or Biological Specimens or
- represents a clinical investigation of a test article involving one or more humans as participants (as defined in 21 CFR 50.3(c), 21 CFR 50.5(j), and 21 CFR 50.5(f) respectively).

The IRB staff may make determinations regarding those projects that do not involve human subjects either by not "engaging" the University in Human Subject Research, by those projects which involve Coded Research per OHRP guidance or those which are Exempt per 45CFR46.101. The UVA IRB's designate the chair, vice chair, chair’s designee (experienced IRB member or experienced IRB staff member) to review the entire application and make the initial determinations regarding the type of review required (full board or expedited review). If the chair, vice-chair or the chair’s designee cannot determine the appropriate level of review, the application will be referred to the full IRB for review.

Additional information may be found at Activities that Require IRB Review. This includes such things as information regarding Quality Improvement vs. Research determinations , use of information in case studies and use of data from Public Data Sets.

All human subject research applications are assigned to full board review unless they meet the criteria for exemption or expedited review criteria.

All projects involving the use of investigational drugs, devices, or biologics for which an IND/IDE is required receive full board review.

DETERMINATION OF NON- HUMAN SUBJECT RESEARCH

Study teams may complete a Determination of Human Subject Research Worksheet that can be submitted to the IRB for review. This worksheet is a guide to help the investigator determine if the activity is human subject research and regulated by the Department of Health and Human Services (DHHS) and/or the Food and Drug Administration (FDA)**.** Activities that meet the definition of human subject research will require submission of an application to the IRB-HSR.

CODED RESEARCH INVOLVING PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS

Additional types of projects may meet the DHHS definition of "Coded Research Involving Private Information or Biological Specimens". In order to meet the DHHS definition the following criteria must be met:

1. The material/data, in its entirety, was or will be collected for purposes other than this project (e.g. the material was or will be collected solely for clinical purposes, or for unrelated research purposes, with no "extra" material collected for the purpose of this project).The person providing the materials/data to the researcher will not otherwise be involved in this project, such as in interpretation or analysis of the data or creation and publication or presentation of research results.
2. The material/ data are given to the researcher with a code. The researcher receiving the specimens/ data will never have access to the key to the code. The code cannot be derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)

If 2 above is checked one of the following is required:

a. The key to decipher the code is destroyed before the research begins
b. A signed agreement is required between the person releasing the specimens/ data and the researcher receiving the specimens/data stipulating the key to the code will never be released to the researcher.
c. Confirmation of IRB approval of written policies and operating procedures for a repository or data management center that prohibit the release of the key to the researchers under any circumstances, until the individuals from whom the information or specimens were collected are deceased.

If your project meets the criteria of "Coded Research Involving Private Information or Biological Specimens"- an alternate submission process is required via protocol builder.

DETERMINATION OF EXEMPTION

Investigator Responsibilities

- A claim of exemption means that the researcher believes that a proposed research activity meets exemption criteria.
- In order to fulfill requirements for the proper review of research, investigators cannot "self-exempt" from IRB review.
- In order for the designated IRB staff member to make this determination, the PI must submit the appropriate application for IRB review.
- Studies that meet exemption criteria do not necessarily mean that the investigator is exempt from informed consent or HIPAA requirements.
- The exemption granted is only for the protocol as written at the time of the initial review when the decision to exempt was determined.
- Investigators who conduct research exempt from IRB oversight must report changes in their protocol and receive confirmation from the IRB before implementing the changes.
- If the protocol remains exempt, the investigator will be notified of the decision. If the change(s) require(s) that the research be reviewed using expedited or full board review, the investigator will be notified and asked to submit the appropriate additional documentation for this review.

IRB Responsibilities and Process

- The IRB is obligated to review all such activities, whether funded or not, and certify that the research meets the federal, state, local and IRB requirements for exemption.
- The IRB has determined that the review and determination of exemption status will be performed by an experienced IRB staff member.
- Research will be determined to be exempt only when the sole involvement of human subjects will be in one or more of the categories listed in 45 CFR 46.101(b)(1-6) or 21 CFR 56.104(a-d). The IRB will not create new categories of exempt research.
- The IRB staff member will
    - not consider any research exempt that involves prisoners (Except certain epidemiological research under category 4 that may qualify for exemption), sensitive aspects of subject's behavior, sensitive surveys, or that takes place in settings where subjects have a reasonable expectation of privacy.
    - not consider any research exempt that involves survey or interview procedures or observation of public behavior of children except for research involving observation of public behavior when the investigator(s) does not participate in the activities being observed.
    - not consider any research exempt that involves a test article regulated by the FDA unless the research meets the criteria for exemption described in 45 CFR 46.101(b)(6).
    - review the proposed research and will validate or decline the investigator's claim for exemption, ensure that risks to individuals are minimized, and confirm that the research meets ethical standards.

- The IRB will document the review and action of the IRB staff member including the category specified in 45 CFR 46.101(b)(1-6) or 21 CFR 56.104(a-d) justifying the classification of exempt.
- The IRB will promptly notify the PI in writing/email of its decision regarding the research.
- If it is determined that the research is not exempt or if modifications are required such as submission of a consent document or strengthening of protections in place to minimize risks to participants, the IRB will include in its written notification a statement of the reason for its decision and give the PI an opportunity to respond in person or in writing. Final approval of exempt research is pending resolution of all minor modifications identified by the IRB reviewer.
- If the IRB staff member determines that an application does not qualify for exemption, the application will be processed either through Expedited Review or by Full Board review. The PI will be notified and instructed to modify the protocol and submit a new application.

Exempt Criteria

Unless otherwise required by the IRB, research activities designated in 45 CFR 46 or 21 CFR 56.104(ad), in which the only involvement of human subjects will be in one or more of the following categories, may be considered by exempt review by the IRB:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. Educational research proposals are exempt providing all of the following are met:
    a. All of the research is conducted in a commonly accepted educational setting (e.g., a private or public school).
    b. The research involves normal educational practices (e.g., comparison of instructional techniques).
    c. The study procedures do not entail a significant deviation in time or effort from those educational practices already existent in the study site.
    d. The study procedures do not involve an increase in the level of risk or discomfort beyond
    e. normal, routine educational practices, including physical education.
    f. The study procedures do not involve deception or withholding of information.
    g. The study procedures do not involve sensitive topics, such as sexual behavior of individual subjects.
    h. A sensitive survey is one that deals with socially questionable or highly personal issues or alcohol and/or drug abuse.
    i. Provisions are made to ensure the existence of a non-coercive environment for all students, including those who choose not to participate.
    j. The school or other agency grants written approval for the research to be conducted.
    k. Educational tests of (i) knowledge, (ii) mastery, or (iii) skills.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i)

information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) (b) of this section, if: (a) the human subjects are elected or appointed public officials or candidates for public office or (b) Federal statue(s) require(s) without exception that the confidentiality of the personally identifiable information be maintained throughout the research and thereafter. Copies of the informed consent form and questionnaire or survey instrument(s) to be used must be forwarded to the IRB for review.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs. This category may also be applied to service/program evaluations of State, city or county programs providing: (a) the program being studies delivers public benefits or services; (b) there is specific statutory authority over the program; (c) there is no statutory requirement that the program evaluation plan be reviewed by an IRB; and (d) there is no significant intrusion or invasion of the privacy of the participant.
6. Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed; (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Services of the U.S. Department of Agriculture. The following categories of clinical investigations regulated by the FDA (21 CFR 56) are exempt from the requirements of this part for IRB review:
    a. Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.
    b. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.
    c. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

Breach of Confidentiality

Additional consideration for exemption includes whether there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review of exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of subject identifiers may be a decisive factor in determining if a study may be considered exempt.

Questionnaires/Surveys/Interviews

Questionnaires or surveys covering sensitive topics may qualify for a Claim of Exemption if they fulfill the following:

- anonymity of the subject is guaranteed,
- potential subjects are fully informed of the sensitive nature of the topics prior to their participation,
- the study does not exceed minimal risk; and
- children are not involved as subjects.

Existing Data, Documents, and Human Biological Specimens

Research involving existing data, documents and/or specimens is typically exempt under Exempt Category 4 as long the following conditions pertain:

- The data, documents and/or specimens exist prior to the conceptualization of the research project. OHRP indicates that the term **"existing**" refers to data, documents, biological material and/or tissue "archived" or "on the shelf" prior to the conceptualization of the research project and prior to review by the IRB.
- The data, documents and/or specimens are publicly available. Data, documents and/or specimens whose access is restricted to select groups are not publicly available.
- The information from the data, documents and/or specimens must be recorded in such a manner that subjects cannot be identified directly, or through identifiers linked to the subjects.
- The researcher must provide written confirmation to the IRB that permission for the use of data, documents and/or specimens has been granted by the gatekeeper and that the information is publicly available.

Protocols Not Eligible for Exemption

Specimen Protocols

The following types of studies would NOT be exempt from review by the IRB:

- Material or tissue that has not been archived prior to the submission of the research protocol to the IRB

- Research with residual material where the investigator intends to identify the subject/subject donor with the acquired sample, either for future purposes or with the intent that the research results may have implications for diagnostic or clinical decisions
- Requests for additional material, i.e., blood, tissue, bodily fluid, from a subject or subject who is scheduled for a diagnostic or clinical procedure. IRB review is required regardless of the amount of extra material requested and regardless of the purpose for which it is procured.
- Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not pre-existing or "archived".

Certain Research Involving Children

Research that involves children and falls into categories 1 - 6 described above under Exempt Criteria may be found to be exempt by the IRB.

However, the exemption category 2 at 45 CFR 46.101(b)(2), pertaining to survey or interview procedures or observations of public behavior, does not apply to research involving children, except for research involving public behavior when the Investigator does not participate in the activities being observed.

Research Involving Prisoners

Research under Exempt Criteria categories 1-3, 5 & 6 is not exempt if it involves prisoners. These applications must be submitted for IRB review. However, certain epidemiological research under category 4 may qualify for exemption.

Observational Research

Observational research involving sensitive aspects of subjects' behavior, or in settings where subjects have a reasonable expectation of privacy, is not exempt.

In addition, observation of children is not exempt from IRB review if the researcher participates in or influences the observed activities.

Sensitive Research

Sensitive survey research is seldom exempt from IRB review (see below for exceptions). A sensitive survey includes questions about illegal activities, or highly personal aspects of the subject's behavior, life experiences, or attitudes.

Examples include chemical or substance abuse, sexual activity or attitudes, sexual abuse, criminal behavior, sensitive demographic data, detailed health history, etc.

The potential for provoking a negative emotional reaction from subjects is a principal determining factor in sensitive survey research.

Projects involving classified research cannot be completed by exempt review.

IRB Oversight of Exempt Studies

The IRB retains the right to require oversight and continuing review when warranted by the nature of the research and/or inclusion of vulnerable subject populations even though it may not be required by federal regulation.

This right may be exercised in situations when the IRB:

a. Has sufficient reason, through anonymous reports, to suspect that the research is not being conducted as described in the submitted protocol and no modifications to the protocol have been received noting changes in the protocol,

b. Receives a complaint from a subject about the conduct of the research,

c. Receives a complaint from another investigator or associate of the researcher,

d. Believes that the research, while meeting the exempt research criteria, could unfairly embarrass individuals, the University or the University's research affiliates,

e. Have other reasons yet to be determined.

Modifications to Exempt Studies

If the researcher wishes to modify the procedures in a project approved under Exempt review, they must submit the modification to the IRB so that the IRB can determine if the project still meets Exempt criteria. The modification may not be implemented until the IRB has reviewed the change. Follow the Process for Modifications.

NON ENGAGED IN HUMAN SUBJECT RESEARCH

Certain types of projects meet the DHHS definition of "Not Engaged in Human Subject Research". Common example of this type of project are described below and are taken from OHRP guidance.

> *You are collaborating with a colleague from another institution and your colleague is sending you data or specimens without any HIPAA identifiers (see below). The data/specimens will be/were collected for the same research project on which you are collaborating. Your colleague may keep a key to the code which could identify the subject from whom the data or specimen was collected- but will never share the subjects' identity or HIPAA identifiers with you.*
>
> *You obtain blood through a blood draw or collect urine and provide such specimens to investigators at an outside institution as a service.*

EXPEDITED REVIEW

The Secretary, DHHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure.

The categories in this list apply regardless of the age of subjects, except as noted.

The IRB chair, vice chair or member designee in accordance with the requirements set forth in 45 CFR 46.110 will review the protocol submission and determine if the research meets the criteria for expedited review.

In reviewing the research, the reviewers may exercise all of the authorities of the IRB, except that the reviewers may not disapprove the research. When a reviewer cannot approve the research under expedited review, the study is remanded to the full IRB for review at a future IRB meeting.

The UVA IRBs will keep members advised of protocols approved by expedited means by providing written documentation of all expedited approvals at full board meetings and note this in the meeting minutes.

Categories of research that may be reviewed by the IRB through an expedited review:

Research activities that

(1) present no more than minimal risk to human subjects, and

(2) involve only procedures listed in one or more of the following categories may be reviewed by the IRB through the expedited review procedures authorized by 45 CFR 46.110 and 21 CFR 56.110.

The activities listed should not be deemed to be of minimal risk simply because they are included on this list.

Inclusion of this list merely means that the activity is eligible for review through the expedited review procedures when specific circumstances of the proposed research involve no more than minimal risk to human subjects.

Though the Federal regulations state that the categories in this list apply regardless of the age of the subject, the vulnerable population stipulations still apply.

Investigators are reminded that the standard requirements for informed consent apply regardless of the type of review utilized by the IRB. Expedited review procedures do not release the investigator from the obligation of obtaining informed consent or authorization from human subjects enrolled in the research.

The categories eligible for expedited review in accordance with 45 CFR 46. 100 and 21 CFR 56.110 are:

1) Clinical studies of drugs and medical devices only when conditions (a) or (b) is met:
    (a) Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks associated with the use of the drug is not eligible for expedited review.)
    (b) Research on medical devices for which
        i. an investigational device exemption (IDE) application17 is not required; or
        ii. the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2) Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:
    (a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period, and collection may not occur more frequently than two times per week; or
    (b) From other adults and children considering the age, weight, and health of the subjects, the collection procedure, the amount of blood collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than two times per week.
3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
    (a) hair and nail clippings in a non-disfiguring manner;
    (b) deciduous teeth at the time of exfoliation or if routine subject care indicates a need for extraction;
    (c) permanent teeth if routine subject care indicates a need for extraction;

(d) excreta and external secretions (including sweat);

(e) uncannulated salvia collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a diluted citric solution to the tongue;

(f) placenta removed at delivery;

(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during delivery;

(h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(i) mucosal and skin cells collected by buccal swab, skin swab, or mouth washings;

(j) sputum collected after saline mist nebulization.

(k) vaginal swabs that do not go beyond the cervical os

(l) rectal swabs that do not go beyond the rectum

(m) nasal swabs that do not go beyond the nares.

4) Collection of data through non-invasive procedures (not involving general anesthesia or sedation) employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples of non-invasive procedures that may qualify for expedited review are

   (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve the input of significant amounts of energy into the subject or an invasion of the subject's privacy;

   (b) weighing or testing sensory acuity;

   (c) magnetic resonance imaging;

   (d) electrocardiograph, ultrasound, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, diagnostic infrared imaging, doppler blood flow, and echo-cardiography;

   (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5) Research involving materials (data, documents, records or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment and/or diagnosis). (Note: Some research in this category may be exempt from IRB regulations for the protection of human subjects (45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

6) Collection of data from voice, video, digital or image recordings for research purposes.

7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation,

human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from IRB regulations for the protection of human subjects 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8) Continuing review of research previously approved by the IRB as follows:
   (a) where
      i. the research is permanently closed to the enrollment of new subjects;
      ii. all subjects have completed all research-related interventions; and
      iii. the research remains active only for long-term follow-up of subjects; or
   (b) where no subjects have been enrolled and no additional risks have been identified; or
   (c) where the remaining research activities are limited to data analysis.
9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened full IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Types of studies and the amount of review:

Risk	Amount of Review	Types of studies
No greater than Minimal risk and procedure fits under an expedited review category	Expedited	• Blood draw (*minimal amount as required by expedited category*) from needle stick or peripheral catheter • ECGs • physical exam • standard psychological testing • epidemiological studies • use of otherwise discarded tissue obtained during a clinical procedure for clinical purposes (*no extra tissue, fluid etc. taken for the research)* • nutritional assessments • surveys or questionnaires of a non-sensitive nature • chart reviews and keeping HIPAA identifiers • use of data from an existing database • use of banked specimens for minimal risk research (*e.g. not testing of polymorphisms)* • database is being developed that contains data gathered from existing sources such as the medical record • where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable , HOWEVER, appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal AND documentation of the application for a Certificate of Confidentiality is submitted prior to approval. (S*ee Certificate of Confidentiality information on the IRB-HSR website)*
Minimal Risk however the procedure does NOT fit under an expedited category	Full Board	• small amount of additional fluid, tissue is being collected for research purposes and the collection method itself presents greater than minimal risk (*collection of additional CSF, biopsy tissue etc)* • randomization to one of several approved drugs/devices • trials with procedures such as indwelling catheters • oral glucose tolerance test • induced sputum, • skin biopsy • imaging studies (except MRI without contrast)

Greater than Minimal Risk	Full Board	• collection of identifiable sensitive information without a Certificate of Confidentiality • clinical trials of an investigational drug • studies that involve randomizing to a placebo group • anything is being ingested, injected or implanted or sprayed into the body such that systemic absorption will occur, even if the item being used is not the item under study. • anything is being introduced into an orifice solely for research, *Examples: pap smears, ear probes that are inserted further into the ear than the entrance of the auditory canal; rectal swabs, anything being placed into the nose farther than a finger could go* • blood samples for research are being collected from a central or arterial line (whether existing or placed for research) • additional CSF is being collected from an existing shunt or externalized CSF drain. • endoscopy • lumbar puncture • bone marrow biopsy • therapeutic intervention trials involving procedures such as insulin clamp or organ biopsies • studies involving subjects with illnesses begin treated with study procedures that may result in moderate to severe adverse events • assessments, surveys or questionnaires of a sensitive nature where HIPAA identifiers will be retained • databases that contain sensitive information that is identifiable **and** NO Certificate of Confidentiality will be sought • clinical trials of diseases where the endpoints are major morbidity or mortality • assessment of serious toxicity requiring comparison of toxicity rates • implantation of a device with an IDE • use of a new chemical or drug for which there is limited or no available safety data in humans • gene transfer • multicenter trials involving greater than minimal risk to subjects • high risk clinical procedures if performed solely for research purposes • classified research involving human subjects • where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable AND no documentation of the application for a Certificate of

		Confidentiality is submitted prior to approval. (S*ee Certificate of Confidentiality information on the IRB-HSR website* • subjects are being randomized to different standard of care treatment groups and the standard of care present greater than minimal risk. (For example: the standard of care involves treatments with drugs or devices (whether approved or not approved). *(See Attachment # 1 of this document for more information.)* • subjects receiving any ionizing radiation exposure (any scan except Ultrasound and MRI). Imaging studies requiring the injection of contrast for research purposes • the research involves some form of deception, • information about participants is obtained from a third party, • the researcher, or a research assistant, is in a position of power over the participants (e.g., an instructor or professor), • there is potential for participants to perceive coercion to participate in the research (e.g., the professor will find out whether students participated in the research, there is a very high payment for participating),

FULL IRB REVIEW

If a protocol does not meet any other type of review approval (see Non Engaged, Coded Research, Exempt and Expedited) the protocol will be reviewed by the Full Board.

Submissions requiring full board review must be received by the submission deadline posted on the IRB website for consideration at the next scheduled IRB meeting.
Currently, Biomedical IRB (IRB-HSR) meetings are held the second and fourth Tuesday of the month except for December when only the first meeting is held. Any biomedical research project involving human subjects, regardless of its source of funding, is reviewed by the Biomedical IRB.

URGENT REVIEW OF APPLICATIONS

Urgent review procedures may be invoked only under unusual circumstances. This does not include urgency that is a result of negligence or delay on the part of the investigator or his/her staff to submit human subjects research applications in a timely fashion.

On occasion, however, an investigator is faced with an immediate deadline beyond his or her control. If the chair permits urgent review of a protocol, the materials are distributed as soon as possible to IRB members to allow sufficient time for review prior to the meeting. The investigator may be required to attend the meeting to answer any questions that arise. If approved, the approval documentation is completed as per any other approval.

APPEAL PROCESS

Only the full board can NOT approve a study. If a coded, non-engaged, exempt submission or an expedited protocol is not approved by the Chair or their designee, the investigator may take the protocol to the full board for review. If the IRB-HSR votes to disapprove a protocol or to suspend or terminate research, a principal investigator may appeal the decision by writing a letter to the IRB-HSR requesting reconsideration. If after considering an appeal, the Board reaffirms the previous decision no further appeal can be considered. The Associate Vice President for Research will be kept informed of the fate of any such appeals, but does not have the authority to over-rule the final decision of the IRB-HSR.

RESPONSIBILITIES OF PRINCIPAL INVESTIGATORS

Investigators should be aware of certain, specific responsibilities that are required when conducting research.

Plans for human research should reflect careful and unhurried consideration on the part of the investigator, in terms of what questions he/she proposes to answer and the precise methodology needed to obtain those answers.

Although most investigators are familiar with some of the paperwork requirements associated with research, there are many reporting requirements which are often overlooked by investigators until problems are encountered with respect to a certain research activity.

It is important for investigators to prepare and maintain clear documentation of research activities in an attempt to minimize or alleviate unnecessary confusion which may arise during the performance of research and during the course of routine audits carried out by the IRB, the FDA or other sponsoring or regulatory bodies.

The Investigator signs an Investigator Agreement and submits this to the IRB with the new protocol application. If a sub-investigator /coordinator on the protocol is not a UVA employee, they should sign an Unaffiliated Investigator Agreement and submit this to the IRB with the new protocol application. The Investigator Agreement /Unaffiliated Investigator Agreement is kept on file in the IRB office with the specific study file.

QUALIFICATIONS FOR PRINCIPAL INVESTIGATOR

The University of Virginia IRB's have set criteria for determining who may be the Principal Investigator on grants and protocols. Eligibility requirements differ between protocols and grants.

IRB-HSR Investigator Agreement

IRB-HSR Unaffiliated Investigator Agreement

IRB REQUIRED SUBMISSIONS

Please refer to Types of Submissions to the IRB.

CONFLICTS OF INTEREST

In the preparation of the protocol the researchers should carefully consider whether a conflict of interest exists.

Conflict of Interest may be defined as a set of conditions in which an investigator's judgment concerning a primary interest (e.g., subject welfare, integrity of research) could be biased by a secondary interest (e.g., personal or financial gain).

A conflict of interest may create a bias in judgment. It may be further described as situations where the potential for bias is such that decisions may be called into question. It depends on the situation, and not on the character or actions of the individual.

Federal guidance and University of Virginia policy require that all conflicts of interest be revealed to potential research subjects in the consent form.

Additional management strategies may also be required based a review of the conflict of interest to the Conflict of Interest Committee.

The following are examples of situations considered to involve a conflict:

- Investigator, investigator's spouse or anyone else in their immediate family owns more than 3% share of stock in the sponsoring company or receives more than $10,000 a year in income from the sponsor of the study
- Investigator holds or has applied for patent on investigational drug, device or intellectual property
- Investigator invented the device
- Investigator serves on an advisory board or gives lectures for the company sponsoring this protocol
- If there is a complex relationship with the sponsor, that might give the appearance of a conflict to someone outside the project
- If any of the previous examples might be true for relationships with a competitive companies drug or device

<u>The following are examples of situations considered not to involve a conflict.</u>

- UVa will receive payment from the sponsor for conducting a clinical trial
- The investigator will author a paper about the results of the research.

Financial Conflict of Interest

Financial conflicts of interest occur when one or more researchers have a significant financial interest in the research which is proposed.

Significant financial interest does not refer to receiving funding to cover the costs of conducting the research.

Rather, a conflict of interest exists when an independent observer may reasonably determine that the significant financial interest may affect or appear to affect the design, conduct, management or reporting of the research.

RESEARCH FILES

Principal investigators are required to maintain a research file.

A research file may consist of paper, electronic and/or other media.

The requirements for a research file include, but are not limited to:

- all correspondence with the IRB and the sponsor (if applicable),
- documentation of subject eligibility, and the consenting process, and

- a copy of the signed informed consent form (if applicable) obtained from all subjects participating in and/or who have participated in the protocol regardless of whether or not the subjects completed the study.

The file will act as the investigator's documentation regarding proper performance of the study.

This information may be reviewed by the IRB, Federal or local authorities, sponsors, and other authorized individuals to ensure proper performance of the study.

Faculty advisors are required to maintain research files for student research completed under their direction.

PRIVACY AND CONFIDENTIALITY

Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information of all human subjects participating in research, except as required by law or released with the written permission of the subject.

Those who conduct research under an UVa IRB approved protocol must develop a plan in each protocol to protect the privacy and confidentiality of subjects.

Subjects have the right to:

- be protected against invasion of their privacy,
- expect that their personal dignity will be maintained, and
- expect the confidentiality of private information will be preserved.

The more sensitive the research, the greater the care is required in obtaining, handling, and storing the data.

The conditions for maintaining confidentiality of the subjects and the research records are required for the life of the data.

Identifiable Personal Information

No single item (except possibly a person's Social Security Number, which by law cannot be used except for very specific circumstances) can be relied upon to identify an individual with certainty.

Names, addresses or telephone numbers may more directly identify an individual than postal codes, date of birth, age, occupation, initials, hospital or student number, ethnic group or religion.

Although individual items may not by themselves permit identification of an individual, taken together in a given context and with a certain amount of effort and use of other sources, a combination of items may allow an individual to be identified.

This means that all items of information relating to an individual may have the potential to identify that individual.

Privacy

Privacy is the right of persons not to share information about themselves.

Researchers have a duty to respect the privacy of prospective subjects. That is, the researcher allows the research subject to determine when, how, and to what extent information about him or her is communicated to others.

Researchers usually protect an individual's right to privacy by obtaining free and informed consent before collecting personal information about him or her.

The act of contacting potential subjects to seek free and informed consent to access private information may constitute a breach of privacy if the investigator does not have access to such individuals in the course of his or her usual professional activities.

In general, someone the research subject would think has a reason to know why he or she might participate in the study should be the first to approach the research subject or that person should be identified in any communication to a potential subject.

Confidentiality

Confidentiality is the obligation to keep private information that has been collected from being shared with others.

Researchers have a duty to respect the confidentiality of personal information collected during research.

Research projects vary substantially in:

- the sensitivity of the information involved,
- the possibility of identifying particular individuals, and
- the magnitude and probability of harms that may result from identification of research subjects.

Breaches in confidentiality may also have a negative impact on family and friends or the group to which the research subject belongs.

The researcher has a duty to protect research subjects from harm through unauthorized release of identifiable personal information.

Confidentiality safeguards include:

- assigning each research subject a code number and using that number on all data about the subject, and
- use of locked rooms and filing cabinets for storage of data.

Anonymity

When information collected through research is disseminated, research subjects normally are de-identified, unless identification has been agreed to or requested by the research subject.

Often, data are presented in aggregate form which also reduces the potential to link specific responses to individuals.

Limits

In some instances, research results may be disclosed to

- government agencies
- the research sponsor
- the IRB or its designees
- a regulatory agency
- those individuals who may be responsible for financial oversight at the institution where the research is conducted.

State statutes may require reporting of

- child abuse
- sexually transmitted diseases
- intent to murder
- suicidal thoughts

In some cases it may be impossible to present the data without identifying the research subject. Examples include:

- those involving well-known individuals,
- those with very rare conditions, or
- research that requires presentation of photographs or videotapes.

Research subjects need to be aware of any limitations to anonymity in these situations.

In other cases, research records may be liable to subpoena in judicial and administrative proceedings, and data may be vulnerable to search warrants.

Because researchers have a duty to protect the confidentiality to the extent possible within the law, it is legitimate for the researcher and the institution to argue the issue in court. In fact, this may be the only legal option open to a researcher to protect the confidentiality of research data.

Guidelines for Protecting Confidentiality

Investigators are encouraged to adopt the following principles in order to protect the confidentiality of subjects participating in research. In addition, there are several University and Health System Policies, Guidance and Procedures which must be followed. These are specified in your protocol. The following includes a summary of requirements to comply with UVa Health System, Medical Center and University Policies and Guidance.

> ***Highly Sensitive Data*** *is:*
> *-personal information that can lead to identify theft if exposed or*
> *-health information that reveals an individual's health condition and/or history of health services use.*
>
> ***PHI-*** *a type of Highly Sensitive Data, is health information combined with a HIPAA identifier*

- LIMIT- Limit the HIPAA identifiers to the minimal amount needed- e.g. use initials instead of name, use a code instead of initials, limit amount/type of health information collected, and collect and share only those items you state you will in this protocol.
- SECURE- Secure Highly Sensitive Data
  - Because single-use electronic devices and media, such as desktops, laptops, memory sticks, CDs, smartphones etc., can be easily lost or stolen, the University strictly limits the circumstances under which Highly Sensitive Data may be stored on them. In accordance with the University's Electronic Storage of Highly Sensitive Data Policy, you must obtain written approval from your Department AND VP or Dean prior to moving data to single use devices or media by using the Highly Sensitive Data Storage Request Form.
    - *You additionally are responsible for applying all security safeguards covered in that policy, including but not limited to password protecting and encrypting any document on a single access electronic device.*

- *If you use your smartphone to send email and your phone is not managed was not purchased and/or set up for you by the Health System, you cannot send Highly Sensitive Data via email.*
  - *In addition, do not use Outlook Web to send your email if it contains sensitive data.*
  - *Also, you are not allowed to auto forward your email to outside email systems like Gmail or Yahoo.*
  - *Do not save any email attachment containing Highly Sensitive Data to a single use device.*
- *You are allowed to access Highly Sensitive Data stored on the University or Health Systems network via a VPN, however you cannot download any of the information onto your desktop or laptop.*
- *Store files containing Highly Sensitive Data on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the "F" and "O" managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive.*
- *If data will be collected and/or viewed via a website, it is critical that the website and associated data file are set up in a highly secured manner. Do not attempt without assistance from:*
  University Side: ITCmicrosystems@virginia.edu
  Health System: Web Development Center: (434-243-6702)

- Encrypt any electronic file containing Highly Sensitive Data that is not on a network drive specifically designated for this purpose. . *See encryption solutions guidance.*
- Password protect any electronic device containing Highly Sensitive Data.
- Lock up hard copies of Highly Sensitive Data.

- PROTECT- Protect Highly Sensitive Data
  - Do not leave a hard copy file open on your desk when not using it and secure your computer when not attended.
  - Have discussions in private.
  - If you lose Highly Sensitive Data, you must report it in accordance with the Information Security Incident Reporting Policy.
  - Do not share Highly Sensitive Data with those not on the study team or those who do not have a need to know.
  - Do not share with sponsor unless subject has already signed a consent form or IRB has approved waiver of consent.
  - If faxing Highly Sensitive Data
    - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
    - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
  - Highly Sensitive Data may not be stored in a Drop Box.
  - If you plan to store data in the Cloud, you must consult with UVa Information Technology Services (ITS) to verify all essential security measures are in place. If you have a contract to use the cloud, the contract must include required security measures as outlined by ITS.

- DO NOT email health information with name, medical record number or Social Security number to or from an email address that does not have an *HS in the address. May use subject initials if within the UVa HIPAA covered entity: The "UVA HIPAA covered entity" includes the hospital, health system, School of Medicine School of Nursing and the VP for Research Office.
- Be aware: PHI collected without consent/ HIPAA authorization will NOT be allowed to leave UVa in an identifiable form unless the disclosure is tracked with Health Information Services.
- Any Highly Sensitive Data sent outside of UVa (e.g. to sponsor) that was obtained under a consent must be encrypted and password protected.
- If your electronic device is sent outside of UVa for repair, all institutional data, whether Highly Sensitive or not, must be either encrypted or removed.
- If transporting Highly Sensitive Data in paper format from one UVa building to another, take the following steps to protect it:
    1. Put paper inside a closed container such as a briefcase, or sealed envelope to limit the chance of a losing a piece.
    2. Do not leave Highly Sensitive Data unattended in a public area if it is not locked up.
- When the study is complete, all electronic files containing Highly Sensitive Data must be stored on a network drive specifically designated for that purpose. They may not be stored on a single use device such as a CD.

- STOP, THINK and BE CAREFUL-
    - If this was your Highly Sensitive Data how would you want it protected?
    - There are significant monetary fines to the individual and the institution for loss or misuse of sensitive data.
    - Your job may also be on the line.

Certificate of Confidentiality

Data collection about sensitive issues (such as illegal behavior, alcohol or drug use, or sexual practices or preferences) requires the protection of confidentiality beyond preventing accidental disclosures.

Under Federal law, researchers can obtain an advance grant of confidentiality, known as a Certificate of Confidentiality that will provide protection against compulsory disclosure, such as subpoena, for research data.

The Certificates of Confidentiality were developed to encourage participation in research by granting certain protections to a subject divulging possible compromising information.

The Certificates, however, do not exempt investigators from performing ethical research nor do they allow investigators to abdicate the responsibility to act in the public good.

Therefore, investigators are required to include a statement in the consent form that alerts potential subjects of the legal and ethical mandate compelling researchers to report certain criteria.

The investigator should delineate in the IRB protocol any conditions under which confidential information might be disclosed and create an informed consent document that accurately reflects those conditions, including any voluntary disclosure by the researcher.

The IRB is required to determine whether the risks to subjects are minimized, informed consent is appropriate, and privacy and confidentiality protections are adequate.

Certificates are issued only "when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives."

The Public Health Service policy defines "sensitive" research as involving the collection of information falling into any of the following categories:

- Information relating to sexual attitudes, preferences, or practices;
- Information relating to the use of alcohol, drugs, or other addictive products;
- Information pertaining to illegal conduct;
- Information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
- Information that would normally be recorded in a subject's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination;
- Information pertaining to an individual's psychological well-being or mental health.
- Information in other categories not listed may also be considered sensitive because of specific cultural or other factors, and protection can be granted in such cases upon appropriate justification and explanation.

Additional policy considerations apply to research that involves the collection of data that relates to communicable diseases. The Assistant Secretary of the Department of Health and Human Services has issued a policy granting certificates of confidentiality to projects that "intend routinely to determine whether its subjects have communicable diseases and that are required to report them under State law." Certificates will be issued:

- where the referring and/or treating physician assures the project director that they have complied with reporting requirements; or
- where there is no referring and/or treating physician, the investigator has reached an agreement with the health department about how s/he will cooperate with the department to help serve the purposes of the reporting requirements (Unless the investigator can show why such cooperation is precluded; and
- only where disclosures of identifiable information about subjects comply with regulations on subject protection and are explained clearly to subjects prior to their participation.

STUDENT RESEARCH

Some projects assigned to students in a class may have a research component or constitute training in research methodology. If such projects are intended to contribute to generalizable knowledge (e.g., through publication or dissemination outside the classroom), they are required to undergo IRB review and approval.
Classroom projects that are exclusively for instructional purposes need not undergo review by the IRB. Instructors and students are encouraged to follow Federal and University policy when designing and conducting class projects with human volunteers.

Student initiated research involving human subjects, whether dissertation, thesis or other research projects, must be supervised by a faculty advisor and submitted to the IRB for review.

IRB review and final approval must take place during the proposal stage of the dissertation or thesis.

Additional information may be found under the FAQ found at IRB-HSR Information

NON-COMPLIANCE REPORTING

The principal investigator is responsible for ensuring that s/he and any other co-investigators adhere to the principles and practices for the use of human subjects in research as set forth in Federal Regulation and this Guide including the reporting to the IRB of all know instances of non-compliance.

In the case of student research, it is the responsibility of the faculty advisor to ensure that the policies and procedures of this Guide are followed.

PARTICIPANTS IN HARMFUL SITUATIONS: ABUSE, SUICIDE, AND THREAT OF HARM

Researchers often work with participants who are at-risk for harmful situations in an effort to understand the participants' circumstances and research ways to improve their situations.

However, such study designs are more likely to lead to disclosures about

- abusive relationships,
- suicidal tendencies, and
- threats to harm others.

In such instances, the board will require that additional safeguards be put in place to protect vulnerable participants, such as:

- demonstrating ability to handle such situations,
- obtaining a Certificate of Confidentiality and
- providing specific plans for dealing with an incident.

However, please note that these situations can become evident in studies that would not normally be considered "at-risk". Although the IRB may not require steps for dealing with a participant in a harmful situation, consider how to handle a situation should it arise.

Please become familiar with:

- the signs of a harmful situation
- your responsibilities for reporting a situation
- how to report.

These situations are often complicated and delicate. If you are concerned about a situation and need further guidance, please consider contacting other individuals experienced in handling these kinds of situations. In some situations, you may not have the expertise to best help an individual in crisis and it would be appropriate to refer the participant to someone who can help them.

If your study involves public schools, please see the public school policy section for additional information. Public schools have more specific guidelines for dealing with a crisis situation.

Child Abuse

If your study involves children, especially if you are working intimately with them, there is always the possibility that you could discover evidence of child abuse. It is important to make yourself aware of the signs of child abuse, your reporting responsibilities, and where to report any suspicion. If you are working with at-risk

children, you will need to demonstrate that you are qualified and capable of working with this population, as the Board views these children as particularly vulnerable.

What is child abuse?

For an excellent explanation of child abuse and signs of abuse, please see the Prevent Child Abuse Virginia.

If you are an educator or will work in a school system, **Virginia Commonwealth University** has published an online training site for educators. Although this site is focused on educators, any researcher working with children could benefit from this training.

What are my responsibilities to report child abuse?

The Code of Virginia states that the following individuals are legally obligated to report signs of abuse:

- Persons licensed to practice medicine or any of the healing arts, hospital residents or interns, nurses, or duly accredited Christian Science practitioners
- Teachers or other persons employed in public or private schools, kindergartens, or nursery schools
- Persons providing childcare full-time or part-time for pay on a regularly planned basis
- Social workers, mental health professionals, or any person responsible for the care, custody, and control of children
- Probation officers, law enforcement officers, mediators, or court-appointed special advocates

As a researcher, you may fall into a category that makes you legally obligated to report suspicions of abuse. Failure to report can result in a fine. Regardless of your legal responsibilities, the Board asks that you act in the best interests of the child.

Your ethical responsibilities as a researcher are explained in the Belmont Report. In the "Respect for Persons" section, it states that "persons with diminished autonomy are entitled to protection." In the "Beneficence" section, it states that "Persons are treated in an ethical manner by making efforts to secure their well-being." In your work with children, please seek to secure their well-being by being aware of their situations and where there may be a potential for harm to them. Depending on your expertise, it may not be appropriate for you to council an abused child or to become involved in the family's situation; in some cases, inappropriate action may put the child in a dangerous situation. Please contact the necessary authorities if you are concerned about a child's safety and seek advice from those who are experienced in handling such situations.

Who do I contact if I suspect child abuse?

To report suspected abuse or neglect call the department of social services in the locality in which the child lives or where the alleged abuse has occurred (Charlottesville Social Services: 434-970-3400). You may also call:

Virginia Child Abuse and Neglect Hotline
1-800-552-7096 (voice/TTY)

If you feel that the child is in immediate and severe physical danger, call Child Protective Services (Charlottesville CPS: 434-970-3400) and/or local law enforcement immediately (Charlottesville Police Department: 434-977-9041).

If you are working with a child through a public school, there may be additional reporting protocol required by the school.

Public School Reporting Policies for Child Abuse

Who should report?
Any teacher or other person employed in a public or private school, kindergarten or nursery school is legally required to report child abuse. Beyond legal obligations, please consider your ethical obligation to protect your participants and protect children in general.
How do I report?
Each school district is responsible for developing protocol for reporting child abuse, so you should talk to the principal or school administrator about their policies. Albemarle County School District, for example, requires that the principal be notified about the incident. The principal will then contact the appropriate institutions, such as the Department of Social Services.
For more information about child abuse reporting requirements, please see the Code of Virginia.

Domestic Abuse: Emotional, Physical, and Sexual Abuse of Adults

What is domestic abuse?

Domestic abuse can take many forms from the inward signs of emotional abuse and sexual abuse to the more obvious outward signs of physical abuse. As a researcher, you may encounter both the victim and the victimizer. The Women's Place at UVA has an excellent site that defines emotional, physical, and sexual abuse and provides information on the signs of abuse. This site can be a good resource to provide to your participants if you suspect they may be victims of abuse.
In this section, the discussion of abuse is meant to cover on-going events, or the suspicion of an event that has already occurred. In the event that you become aware of an immediate and specific threat to harm someone, you may have legal obligations to report the event to the authorities.

What are my responsibilities to report domestic abuse?

As a researcher, you do not have specific legal responsibilities for reporting abuse. However, you should consider the well-being of your participants and act in their best interests, as stated in the Belmont Report. Often these situations are delicate and require experienced individuals to council the participant. If you do not have certified experience in helping an abused individual, do not council your participant or become involved in the situation. Inappropriate action may put the participant at greater risk. As you are working with an adult, the more appropriate step may be to refer the participant to resources that can help them, such as a hotline or shelter (as the situation warrants) instead of simply calling the police. However, if you become aware of a specific and immediate threat to harm your participant, or if your participant expresses intentions to harm another, you should contact the appropriate authorities. Please note that mental health service providers have a duty to take precautions to protect third parties from violent behavior or other serious harm when a specific and immediate threat to cause serious bodily injury or death has been communicated.

What should I do if I suspect domestic abuse?

Providing a list of resources for the participant to use is one way to respond to suspicions of domestic abuse. For research focusing on such issues, the Board will require that a list of resources be provided to all participants in the study. The Women's Center Sexual and DomesticViolence services has a list of hotlines and community contacts on their website. They also provide a third party anonymous reporting mechanism for campus related incidents.

Elderly and Adults with Diminished Capacity Abuse

The abuse of the elderly and adults with diminished capacity can take many forms including sexual assault, physical abuse, emotional abuse, and financial abuse. The Adult Protective Services (under the Virginia Social Services office) website outlines the signs of abuse and services available.
For Additional Information: Useful Article

What are my responsibilities to report elderly and adults with diminished capacity abuse?

Although researchers are not specifically listed as a legally obligated reporter, there is a lengthy list of responsible parties.

- **Any person licensed, certified, or registered by health regulatory boards** listed in § 54.1-2503, except persons licensed by the Board of Veterinary Medicine:
    - **Board of Nursing**: Registered Nurse (RN); Licensed Nurse Practitioner (LNP); Licensed Practical Nurse (LPN); Clinical Nurse Specialist; Certified Massage Therapist; Certified Nurse Aide (CNA)
    - **Board of Medicine:** Doctor of Medicine and Surgery, Doctor of Osteopathic Medicine; Doctor of Podiatry; Doctor of Chiropractic; Interns and Residents; University Limited Licensee; Physician Assistant; Respiratory Therapist; Occupational Therapist; Radiological Technologist; Radiological Technologist Limited; Licensed Acupuncturists; Certified Athletic Trainers
    - **Board of Pharmacy:** Pharmacists; Pharmacy Interns; Permitted Physicians; Medical Equipment Suppliers; Restricted Manufacturers; Humane Societies; Physicians Selling Drugs; Wholesale Distributors; Warehousers, Pharmacy Technicians
    - **Board of Dentistry**: Dentists and Dental Hygienists Holding a License, Certification, or Permit Issued by the Board
    - **Board of Funeral Directors and Embalmers:** Funeral Establishments; Funeral Services Providers; Funeral Directors; Funeral Embalmers; Resident Trainees; Crematories; Surface Transportation and Removal Services; Courtesy Card Holders
    - **Board of Optometry:** Optometrist
    - **Board of Counseling:** Licensed Professional Counselors; Certified Substance Abuse Counselors; Certified Substance Abuse Counseling Assistants; Certified Rehabilitation Providers; Marriage and Family Therapists; Licensed Substance Abuse Treatment Practitioners
    - **Board of Psychology:** School Psychologist; Clinical Psychologist; Applied Psychologist; Sex Offender Treatment Provider; School Psychologist – Limited
    - **Board of Social Work:** Registered Social Worker; Associate Social Worker; Licensed Social Worker; Licensed Clinical Social Worker
    - **Board of Nursing Home Administrators:** Nursing Home Administrator
    - **Board of Audiology and Speech Pathology:** Audiologists; Speech-Language Pathologists; School Speech Language Pathologists
    - **Board of Physical Therapy:** Physical Therapist; Physical Therapist Assistant
- **Any mental health services provider** as defined in § 54.1-2400.1;
- **Any emergency medical services personnel** certified by the Board of Health pursuant to § 32.1-111.5;
- **Any guardian or conservator of an adult**;

- **Any person employed by or contracted with a public or private agency or facility** and working with adults in an administrative, supportive or direct care capacity;
- **Any person providing full, intermittent, or occasional care to an adult** for compensation, including but not limited to companion, chore, homemaker, and personal care workers; and
- **Any law-enforcement officer**.

As a researcher, you may fall into a category that makes you legally obligated to report suspicions of abuse. Failure to report can result in a fine. Regardless of your legal responsibilities, the Board asks that you act in the best interests of the participant.

Your ethical responsibilities as a researcher are explained in the Belmont Report. In the "Respect for Persons" section, it states that "persons with diminished autonomy are entitled to protection." In the "Beneficence" section, it states that "Persons are treated in an ethical manner… by making efforts to secure their well-being." In your work with the elderly and adults with diminished capacity, please seek to secure their well-being by being aware of their situations and where there may be a potential for harm to them. Depending on your expertise, it may not be appropriate for you to council an abused adult or to become involved in the family's situation; in some cases, inappropriate action may put the adult in a dangerous situation. Please contact the necessary authorities if you are concerned about an adult's safety and well-being.

Who do I contact if I suspect elderly and adults with diminished capacity abuse?

The Adult Protective Services (under the Virginia Social Services office) has a hotline for reporting abuse: 1-888-832-3858

Specific and Immediate Threats to Cause Bodily Injury or Death to a Third Party

What is a Threat?

During your interaction with a participant, you may learn of a specific and immediate threat to hurt or kill someone. A threat can vary in degrees of serious intent. A participant may casually complain about someone and threaten physical harm without the serious intent of hurting anyone. The Code of Virginia states that if a mental health care provider "reasonably believes, or should believe according to the standards of his profession, that the client has the intent and ability to carry out that threat immediately or imminently" then the mental health care provider should act.

This section discusses the general responsibilities of researchers and mental health care providers. If you are conducting your study in a public school or among students, please see Public School Policy for more information about the legal responsibilities and protocol for reporting threats and illegal behaviors.

What are my responsibilities to report a threat?

Mental health care providers are legally responsible to report a threat. The Code of Virginia defines a mental health care provider as the following:

- certified substance abuse counselor
- clinical psychologist
- clinical social worker
- licensed practical nurse
- licensed substance abuse treatment practitioner
- marriage and family therapist
- mental health professional

- mental health service provider
- professional counselor
- psychologist
- registered nurse
- school psychologist
- social worker

Although the code does not specifically list researchers, the participant may be considered a client or patient in your care. If the third party is a child, you have additional obligations to protect the child from physical and sexual abuse in general. Please see Child Abuse for more information.
You are not held liable for failing to report a threat if one of the following apply:

1. Breaching confidentiality with the limited purpose of protecting third parties by communicating the threats made by your client to potential third party victims or law-enforcement agencies or by taking any of the actions below.
2. Failing to predict, in the absence of a threat, that the client would cause the third party serious physical harm.
3. Failing to take precautions other than those described below to protect a potential third party victim from the client's violent behavior.

How do I report a threat?

The Code of Virginia states that doing one of the following actions will satisfy your duty to report:

1. Seek involuntary admission of the client under Chapter 8 (§ 37.2-800 et seq.) of Title 37.2.
2. Make reasonable attempt to warn the potential victims or the parent or guardian of the potential victim if the potential victim is under the age of 18.
3. Make reasonable effort to notify a law-enforcement official having jurisdiction in the client's or potential victim's place of residence or place of work, or place of work of the parent or guardian if the potential victim is under age 18, or both.
4. Takes steps reasonably available to the provider to prevent the client from using physical violence or other means of harm to others until the appropriate law-enforcement agency can be summoned and takes custody of the client.
5. Provide therapy or counseling to the client or patient in the session in which the threat has been communicated until the mental health service provider reasonably believes that the client no longer has the intent or the ability to carry out the threat.

Suicide Threat

The Surgeon General stated that there are far more suicides per year than homicides (over 50%), and suicide is the ninth leading cause of death. According to the Surgeon General, there are certain groups more likely to attempt suicide, specifically those with mental and/or substance abuse disorders, but suicide victims include the entire spectrum of population from children to the elderly. Some risk factors are:

- Previous suicide attempt

- Mental disorders—particularly mood disorders such as depression and bipolar disorder
- Co-occurring mental and alcohol and substance abuse disorders
- Family history of suicide
- Hopelessness
- Impulsive and/or aggressive tendencies
- Barriers to accessing mental health treatment
- Relational, social, work, or financial loss
- Physical illness
- Easy access to lethal methods, especially guns
- Unwillingness to seek help because of stigma attached to mental and substance abuse disorders and/or suicidal thoughts
- Influence of significant people—family members, celebrities, peers who have died by suicide—both through direct personal contact or inappropriate media representations
- Cultural and religious beliefs—for instance, the belief that suicide is a noble resolution of a personal dilemma
- Local epidemics of suicide that have a contagious influence
- Isolation, a feeling of being cut off from other people

What are my responsibilities to report a suicide threat?

As a researcher, you do not have specific legal responsibilities for reporting a suicide threat. However, you should consider the well-being of your participants and act in their best interests, as stated in the Belmont Report. Often these situations are delicate and require experienced clinicians to council the participant. If you do not have certified experience in helping a suicidal individual, do not council your participant or become involved in the situation. Inappropriate action may put the participant at greater risk. As you are working with an adult, the more appropriate step may be to refer the participant to resources that can help them, such as a hotline or mental health clinic (as the situation warrants) instead of simply calling the police. However, if you become aware of a specific and immediate threat of harm to your participant, you should contact the appropriate authorities.

If you are working in a public school system, there is specific protocol for reporting suicidal behavior. Please see the Public School Policy section for more information.

How do I report a suicide threat?

If your participants are at-risk for expressing suicidal intentions, you will need to have protocol in place to provide immediate assistance. For example, should a participant express suicidal intentions, or discuss suicidal thoughts and feelings, an experienced clinician should be available to assess the individual's state and refer them to the appropriate resources for help. Please note that some surveys and instruments, such as the BDI-II,

ask participants if they have suicidal thoughts and feelings. Even though suicide may not be the topic of your research, if you are asking these questions of participants, you need to have a protocol in place for addressing affirmative answers.
If a participant has expressed suicidal intentions and you do not have the protocol or expertise to handle this situation, please refer the participant to qualified individuals. For example, if the participant is a UVA student, the Elson Student Health Center provides counseling and emergency care.

CLOSING STUDIES

Principal investigators have the responsibility of informing the IRB when a study has been completed.

A study is considered to be open and active until the investigator has submitted an IRB Closure Form to the IRB.

Investigators will be notified by the IRB at least annually following the initial approval of the research to complete a Protocol Status Report. At these notification intervals, investigators are to submit either a continuation request or a Closure Form.

Faculty advisors for student research have the obligation to ensure that the Closure Form is filed with the IRB in a timely fashion.

When a principal investigator terminates employment or other association with UVA, he or she is obligated to submit a Closure Form to the IRB or formally transfer the protocol to another principal investigator via a modification which is reviewed and approved by the IRB. In very rare cases, the IRB may grant special permission for the departing individual to remain as principal investigator on the project. Cases are reviewed on a case by case basis.

A study may be closed when **all** of the following apply:

- All subject recruitment and enrollment is complete (i.e., no new subject recruitment or enrollment are ongoing)
- All subject specimens, records, data have been obtained (i.e., no further collection of data/information from or about living individuals will be obtained)
- No further contact with subjects is necessary (i.e., all interactions or interventions are complete and no further contact with enrolled subjects is necessary)
- Analysis of subject identifiable data, records, specimens are complete (i.e., use or access to subject identifiable data is no longer necessary. **Note: this includes review of source documents by study sponsors.**

Please complete the Study Closure Form and submit it to the IRB within 30 days of closure of the study.

In order to close your IRB protocol officially, submission of IRB-HSR Closure Form is required.

If you are leaving UVa, you are strongly encouraged to utilize the Exit Checklist.

RECORD RETENTION

Overview

The IRB maintains an official protocol file for each study to meet the University's regulatory obligations for record keeping. The IRB staff is not responsible for maintaining study documents for the researchers, or for providing copies of official documents to research staff. Keeping accurate and complete protocol records is the responsibility of the study team.

Record Retention by Study Teams at UVa

DHHS Regulated Studies

Requirements for record retention vary with

- the type of research conducted,
- provisions of the investigators funding source, and
- the requirements of the investigators professional association.

DHHS regulations do not clearly address the issue of the length of time a principal investigator should maintain research records after completion of all research activities related to a study.

Records should be kept a minimum of two (2) years after submission or publication of the final project report for which the data were collected, whichever is longer.

The guidance states that records should be kept a minimum of two (2) years after submission or publication of the final project report for which the data were collected, whichever is longer.

If a research study involves health information that was not de-identified, the records must be kept for six (6) years from the date the study was closed with the IRB.

If retention requirements specified in a funding agency's regulations are longer, the agency requirements will apply.

In addition, at the discretion of the investigator, some data may be retained longer for use in subsequent projects.

All records must be accessible for inspection and copying by authorized representatives of the IRB, regulatory agencies and sponsor.

FDA Regulated Studies

For studies regulated by the FDA, the investigator or sponsor shall maintain the records during the investigation and for a period of 2 years after the latter of the following dates:

- the date on which the investigation is terminated or completed, or
- the date that the records are no longer required for purposes of supporting a pre-market approval application or
- a notice of completion of a product development protocol.

An investigator or sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them including the

requirements of 21CFR812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

The following guidelines are provided to assist investigators and research staff with recordkeeping of approved IRB protocols documents and to facilitate submissions of correct versions of protocol documents for the life of the study.

Records to Keep While a New Study is Being Reviewed by the IRB

The study team should keep electronic files of all study documents (e.g., protocol, informed consents etc.) in order to make requested revisions that may be required for IRB approval.

Records to Keep Once a Study is Approved by the IRB

Hard Copies

- If applicable: Consent(s) with Approval Stamp. All copies of approved consents must be kept, however, only the most current approved version of the stamped consent form should be used to make copies for enrolling research participants.
- All documents previously submitted to the IRB.
- All documents received from the IRB.

Electronic Copies:

- The electronic file of the currently approved protocol and consent form(s) if applicable should be retained for future IRB submissions such as modifications or continuations.

Protocol Modification Submissions

- The study team must incorporate revisions into the most recently approved electronic file version of the protocol and consent form(s), and other protocol documents, as applicable.
- Note that some studies are modified frequently and the most recent approved version must always be used for each modification request.
- Versions checks of protocols and consent forms are performed routinely by the IRB staff. Revisions submitted on older versions of the protocol or consent cannot be reviewed by the IRB and will be returned for correction.

Continuing Renewal Submissions

- The study team must keep copies of all documents, including the Status Forms, submitted to the IRB at the time of the continuation review.

RESEARCH DESIGN CONSIDERATIONS

The purpose of this section is to provide basic information about the IRB's ethical considerations in reviewing protocols utilizing several study designs. These considerations emanate from a common understanding of medical ethics, which have guided the profession for centuries, and from the federal regulations.

SUBJECT SELECTION

Recruitment and selection of participants must be equitable within the confines of the study. Researchers may not exclude participants on the basis of gender, race, national origin, religion, creed, education, or socioeconomic status. Equitable means "fair or just" and used in the context of selection of subjects, this means that the benefits and burdens of research are fairly distributed.

Research sponsors may offer to pay Investigators or study personnel an additional fee to encourage participant recruitment efforts and the timely or accelerated opening of research studies. These payments are strictly prohibited by IRB policy.

- It is not permissible to pay or accept "finder's fees".
- It is not permissible to accept bonus payments. UVa employees or students cannot accept personal payments from sponsors or other researchers in exchange for accelerated recruitment or referrals of patients.
- Cash or cash-equivalent payment to health care providers for referral of subjects or potential subjects is not permitted.
- Other types of compensation (e.g., books, other non-cash gifts) are also prohibited.

Guidance from Belmont Report
Distributive justice, the third principle of the Belmont Report requires the fair selection of subjects and the equitable distribution of the risks and benefits of research. The systematic selection of subjects because of easy availability, their compromised position, or because of social, racial, sexual, economic or cultural biases institutionalized in society results in an uneven distribution of the benefits and the burdens of research. The IRB will closely examine research that requests recruitment of subjects solely due to their easy availability, compromised position, or susceptibility to manipulation. For example, students, subjects, or laboratory employees are compromised to the extent that their grades, access to health care, or jobs are dependent on those investigators recruiting them for subjects. The protocol should clearly articulate how the recruitment will avoid the appearance of coercion when selecting subjects who are in a dependent relationship to the investigator.

Guidance from National Commission for the Protection of Human Subjects
In order to allow for the fair and equitable distribution of the burden of research and to ensure that certain populations, such as prisoners or subjects in mental institutions, were not recruited solely because of their easy availability, the National Commission for the Protection of Human Subjects recommended a hierarchy of preference in the selection of subjects for research: adults before children; competent individuals before incompetent individuals; non-institutionalized individuals before institutionalized individuals. To adequately assess the risks and benefits of participation in research, the IRB requires accurate information regarding the number of subjects to be recruited and tested. The IRB will closely examine the characteristics of the subject population, such as age, gender, and population diversity outlined in the protocol and the procedures for identifying and recruiting subjects.

Guidance from the NIH
The mandate for the equitable distribution of the risks and benefits of participation in research to include women and minorities was addressed by the NIH in the Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research, published in 1994. The guidelines indicate that

researchers should include minorities and women in study populations, "so that the research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study."

Women and members of minority groups and their subpopulations must be included in all clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the IRB that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

In order to ensure that the burdens of research are evenly distributed, the IRB is required to consider more than the risks associated with the research procedures. The inclusion (recruitment process) of women and members of minority groups and their subpopulations must be addressed in developing a research protocol appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects.

INTERNATIONAL RESEARCH

International research poses unique and complex ethical challenges. As a result, the IRB expects the researcher to acknowledge and understand the following:

- **The researcher must obtain IRB approval before a study can begin.** Whether you are UVa faculty member, staff or student, your research study must be approved by the IRB before it can begin. *To reduce confusion, the researcher should make sure they have the IRB's approval before they leave the country. We suggest the researcher apply to the IRB* ***at least six to nine months*** *before they leave to ensure adequate time for reviews. The researcher should take the written IRB approval with them on their trip.*

- **Demonstrate cultural understanding and sensitivity.** Is the typical process of signing an informed consent document culturally acceptable for the study? Are there other cultural barriers that might be encountered? The IRB protocol should describe any anticipated cultural sensitivities of conducting the research and how the researcher intends to overcome those barriers. The IRB will help develop alternative methods for consent (or other issues) to ensure the research practices are ethically sound and respectful of the culture being studied.

- **Understand the research ethics guidelines of the host country.** Investigators will be required to obtain IRB approval for research done internationally from the UVa IRB and also from the local IRB/Ethics Committee within the country in which they will be doing their research. This approval must be on file with the IRB prior to IRB approval being granted. *The IRB strongly recommends the researcher clearly understand the host country's requirements for reviewing and approving human subject research.* Some countries have clear ethical guidelines that must be met for conducting domestic and/or international research. Other countries will not have a formal process but might rely on other neighboring countries to assist with the review. If the researcher has difficulty determining the existence of an IRB/Ethics Committee in the foreign country, they should contact the IRB.

- **The researcher should contact the IRB while abroad if they encounter any problems or need to change the IRB-approved protocol.** If the researcher finds that upon arrival in the host country, some aspects of the research study must be modified for whatever reason, *please notify the IRB office*

immediately. The IRB will do its best to quickly respond to the notification with further instructions and guidance. Please wait to hear back from the IRB before making any changes to the protocol!**Additional Information on International Research**

IMPLEMENTATION OF HIPAA AND THE PRIVACY RULE BY THE IRB

What is HIPAA?

HIPAA is the acronym for the Health Insurance Portability and Accountability Act of 1996.

The intention of HIPAA is to protect patients from inappropriate disclosures of "Protected Health Information" (PHI) that can cause harm to a person's insurability, employability, etc.

The privacy provisions of HIPAA found in the Privacy Rule apply to health information created or maintained by health care providers who engage in certain electronic transactions, health plans, and health care clearinghouses.

What is PHI?

PHI is information that can be linked to a particular person and that is created, used, or disclosed in the course of providing a health care service (i.e., diagnosis or treatment).

What Does the Privacy Rule Have To Do With Research?

HIPAA affects only that research which uses, creates, or discloses PHI.

Researchers have legitimate needs to use, access, and disclose PHI to carry out a wide range of health research studies.

The Privacy Rule protects PHI while providing ways for researchers to access and use PHI when necessary to conduct research.

In general, there are two types of human research that would involve PHI:

- Studies involving review of existing medical records as a source of research information. Retrospective studies, such as chart reviews, often do this. Sometimes prospective studies do it also, for example, when they contact a participant's physician to obtain or verify some aspect of the participant's health history.
- Studies that create new medical information because a health care service is being performed as part of the research, such as testing of a new way of diagnosing a health condition or a new drug or device for treating a health condition. Virtually all sponsored clinical trials that submit data to the U.S. Food and Drug Administration (FDA) will involve PHI.

What is the IRB's Role?

The IRB-HSR acts as the Privacy Board at UVa to review the use/disclosure of PHI and to determine whether the subjects should sign an "Authorization" (Adds additional language to the consent template) or if a Waiver of Authorization (roughly analogous to a Waiver of Consent under the Common Rule) may be granted. At UVa the requirements for a HIPAA Authorization have been incorporated into the research consent form to eliminate the need for multiple forms. If for some reason a research consent will not be obtained, the IRB-HSR provides a template for a Stand-alone HIPAA Authorization.

Research Provisions of the Privacy Rule

Research Use/Disclosure with Individual Authorization

- The Privacy Rule permits covered entities to use or disclose protected health information for research purposes when the individual who is the subject of the information authorizes the use or disclosure. For clinical trials, authorization must be sought in addition to informed consent. Authorization must also be sought for other research uses or disclosures of protected health information that do not qualify for an IRB waiver of authorization (discussed below).
- The Privacy Rule has a general set of authorization requirements that apply to all uses and disclosures, including those for research purposes. However, several special provisions apply to research authorizations:
    - Unlike other authorizations, which require an expiration date, an authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the end of the research study; and
    - An authorization for the use or disclosure of protected health information for research may be combined with a consent to participate in the research, or with any other legal permission related to the research study (except for research involving the use or disclosure of psychotherapy notes, which must be authorized separately); and
    - Research authorization forms must be filled out completely and accurately by the investigator, to ensure that all parties who require access to protected health information for the research (including sponsors, CROs, DSMBs, IRBs, etc.) are identified in the form and may receive the information. The IRB combined authorization/consent form should be completed by the investigator and submitted to the IRB for review and approval.

Waiver of Authorization for Use or Disclosure of Protected Health Information in Research

Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances. A covered entity may use or disclose protected health information for research when presented with documentation that an IRB has granted a waiver of authorization [See 45 CFR 164.512(i)(1)(i)]. This provision of the Privacy Rule might be used, for example, to conduct records research, epidemiological studies, or other research where de-identified data is unavailable or not suited to the research purpose.

The waiver documentation presented to the covered entity must include the following:

- Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
- A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
- A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
- A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
- The signature of the chair or other member, as designated by the chair, of the IRB or the Privacy Board, as applicable.

The following criteria must be satisfied for the IRB to approve a waiver of authorization under the Privacy Rule:

- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

- an adequate plan to protect the identifiers from improper use and disclosure;
- an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
- adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
- the research could not practicably be conducted without the waiver or alteration; and

- The research could not practicably be conducted without access to and use of the protected health information

Review Preparatory to Research

The Privacy Rule permits a covered entity to use or disclose protected health information to a researcher without authorization or waiver for the limited purpose of a "review preparatory to research."

Such reviews may be used to prepare a research protocol, or to determine whether a research site has a sufficient population of potential research subjects.

Prior to permitting the researcher to access the protected health information, the covered entity must obtain representations from the researcher that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and that protected health information for which access is sought is necessary for the research purpose.

Researchers should consult with UVa Health Information Services (HIS) regarding any forms or applications necessary to conduct a review preparatory to research.
Researchers conducting a review preparatory to research may not record information in identifiable form (see identifiers below), nor may they use the information that they receive to contact potential subjects.

Because the Privacy Rule permits a covered entity to disclose protected health information to the individual who is the subject of the information, covered health care providers and subjects may continue to discuss the option of enrolling in a clinical trial without subject authorization.

Even when permitted by the Privacy Rule, however, any use of subject information for recruitment must comply with IRB recruitment policies.

HIPAA Identifiers

1. Name
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over

89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*

4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security number
8. Medical Record number
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code* .)

Research on Protected Health Information of Decedents

The protections of the Common Rule (45CFR46) apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons ("decedents").

The Privacy Rule contains an exception to the authorization requirement for research that involves the protected health information of decedents.

A covered entity may use or disclose decedents' protected health information for research if the entity obtains representations from the researcher that:

- the use or disclosure being sought is solely for research on the protected health information of decedents,
- that the protected health information being sought is necessary for the research, **and**,
- at the request of the covered entity, documentation of the death of the individuals about whom information is being sought.

Researchers should submit the applicable UVa Health Information Services (HIS) form to HIS when they intend to conduct research involving decedents' protected health information.

Decedent Information with HIPAA Identifiers

If you need to collect information on deceased individuals and also need to record any HIPAA identifier, submit the Decedent Research with PHI: Waiver of HIPAA Authorization Application form to the IRB. The IRB will provide you with an Approval/Assurance Form which may be submitted to Health Information Services to obtain the charts you need.

Limited Data Sets with a Data Use Agreement

When a researcher does not need direct identifiers for a study but does require certain data elements that are not permitted in de-identified data, the Privacy Rule permits a covered entity to disclose a "limited data set" to the researcher without authorization or waiver, provided that the researcher has signed a data use agreement.

The limited data set is still considered to be protected health information, but it must exclude only specified direct identifiers of the individual or of relatives, employers, or household members of the individual.

The research involves a limited data set if the data contains none of the following 16 identifiers:

1. Names
2. Postal address info. (if other than city, state and zip)
3. Telephone numbers
4. Fax numbers
5. Email addresses
6. Social Security #s
7. Medical record, prescription numbers
8. Health plan beneficiary #s
9. Account #s
10. Certificate/license #s
11. Vehicle identifiers (VIN) and serial #s, license plate #s
12. Device identifiers, serial #s
13. Web URLs
14. IP address #s
15. Biometric identifiers (finger prints)
16. Full face, comparable photo images

The recipient must also agree to the following:

- Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
- Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
- Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware; Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
- Not to identify the information or contact the individual.

Accounting for Research Disclosures

The Privacy Rule gives individuals the right to receive an accounting of certain disclosures of protected health information made by a covered entity. See 45 CFR 164.528.

Among the types of disclosures that are exempt from this accounting requirement are:

- Research disclosures made pursuant to an individual's authorization;
- Disclosures of the limited data set to researchers with a data use agreement under 45 CFR 164.514(e).

If required, the accounting must include:

- disclosures of protected health information that occurred during the six years prior to the individual's request for an accounting, or since the applicable compliance date (whichever is sooner), and
- specified information regarding each disclosure.

Multiple Disclosures

A more general accounting is permitted for subsequent multiple disclosures to the same person or entity for a single purpose. [See 45 CFR 164.528(b)(3)].

In addition, for disclosures of protected health information for research purposes without the individual's authorization pursuant to 45 CFR164.512(i), and that involve at least 50 records, the Privacy Rule allows for a simplified accounting of such disclosures by covered entities. Under this simplified accounting provision, covered entities may provide individuals with a list of all protocols for which the subject's protected health information may have been disclosed under 45 CFR 164.512(i), as well as the researcher's name and contact information. Other requirements related to this simplified accounting provision are found in 45 CFR 164.528(b)(4).

Note that each covered entity must have procedures in place to track disclosures of protected health information and to provide accountings to subjects upon request. UVA researchers are required to track their own disclosures of PHI during the course of their research.

HIS Information

The WEB address to Disclosure Trac is: http://hscshisweb1/disclosureTrac/DST_login.aspx
Please note that you will not be able to access this unless you are part of the health system.

Waiver of Informed Consent for Creation of Databases

A covered entity may use or disclose protected health information without individuals' authorizations for the creation of a research database, provided that the covered entity obtains documentation that an IRB or Privacy Board has determined that the specified waiver criteria were satisfied.

Creation of a database of health information for research purposes is regarded as a research activity that requires

- submission of a protocol and
- a consent/authorization form;
- waiver of consent/authorization; or
- an IRB exemption determination.

Protected health information maintained by a covered entity in such a research database could be used or disclosed for future research studies as permitted by the Privacy Rule.

Subjects' Rights to Access Records

With few exceptions, the Privacy Rule gives subjects the right to inspect and obtain a copy of health information about themselves that is maintained by a covered entity or its business associate in a designated record set.

A **designated record set** is basically a group of records that a covered entity uses to make decisions about individuals, and includes a health care provider's medical records and billing records, and a health plan's enrollment, payment, claims adjudication, and case or medical management record systems. While it may be unlikely that a researcher would be maintaining a designated record set, any research records or results that are actually maintained by the covered entity as part of a designated record set (e.g., maintained in the medical record) would be accessible to research participants unless one of the Privacy Rule's permitted exceptions applies.

One of the permitted exceptions applies to protected health information created or obtained by a covered health care provider/researcher for a clinical trial. The Privacy Rule permits the individual's access rights in these cases to be suspended **while the clinical trial is in progress**, provided the research participant agreed to this denial of access when authorizing the use or disclosure of his or her protected health information for the clinical trial. In addition, the health care provider/researcher must inform the research participant that the right to access protected health information will be reinstated at the conclusion of the clinical trial.

Transition Provisions

The Privacy Rule contains certain grandfathering provisions that permit a covered entity to use and disclose protected health information for research after the Rule's compliance date of April 14, 2003, if the researcher obtained any one of the following prior to the compliance date:

- An authorization or other express legal permission from an individual to use or disclose protected health information for the research;
- The informed consent of the individual to participate in the research; or
- An IRB waiver of informed consent for the research.

Even if informed consent or other express legal permission was obtained prior to the compliance date, if new subjects are enrolled or existing subjects are re-consented after the compliance date, the covered entity must obtain the individual's authorization. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization must be sought at the same time.
The transition provisions apply to both uses and disclosures of protected health information for specific research protocols and uses or disclosures to databases or repositories maintained for future research.

Resources

- The UVA Health System also has information regarding HIPAA available on the Health System HIPAA Initiatives website.
- UVA Stand Alone HIPAA Authorization
- Notice of Privacy Practices HIPAA Privacy Rule: Information for Researchers (DHHS/NIH)
- 45CFR Part 160 and 164, Standards for Privacy of Individually Identifiable Health Information; Security Standards for the Protection of Electronic Protected Health Information (HIPAA Privacy and Security Rules)

BIOMEDICAL

AIDS/HIV Related Research

Subjects involved in HIV-related research (HIV-infected persons and persons at risk of HIV-infection) are particularly vulnerable because of their disease status and because the disease disproportionately affects certain populations.

Principal Investigators should be aware of the numerous ethical concerns presented by HIV research, including considerations of confidentiality, privacy and justice and follow Virginia State regulations.

An overriding concern in HIV research is confidentiality and privacy, since breaches of confidentiality could have severe adverse consequences.

In ensuring that research adequately protects subjects' confidentiality, Principal Investigators should consider the following criteria:

- where identifiers are not required by the study design, they are not to be recorded.
- if identifiers are recorded, they should be separated, to the greatest extent possible, from data and securely stored, with linkage restored only if necessary to conduct the research.
- if subjects will be given a fair and clear explanation of how information about them will be handled, including whether and how the information will be recorded in their medical records.
- whether the protocol will specifically set forth how to respond to attempts to force disclosure of subjects' medical records or requests by third parties who have authorizations for disclosure signed by subjects; and
- whether the protocol will clearly state what information will be recorded, who is entitled to see records with identifiers, and whether any state laws require the reporting of HIV infection or the disclosure of other information.

Sharing of HIV Test Results

In research protocols that involve HIV testing, investigators should consider the circumstances under which subjects should or must be told of their HIV sero status. In general, the IRB requires that individuals whose test results are associated with personal identifiers be informed of their HIV test results and provided the opportunity to receive counseling, unless the situation is a special circumstance calling for an exception (*e.g.*, compelling evidence that a given individual would attempt suicide if informed that he/she is seropositive). When individuals will be informed of their HIV antibody test results, Principal Investigators should ensure that the protocol provides for appropriate pre-test and post-test counseling.

Case-Control Studies

One popular type of descriptive study is the case-control study, in which persons with a specific condition (the cases) and persons without the condition (the controls) are selected to participate in the study. The proportions of cases and controls with certain characteristics (*e.g.*, exposure to a particular drug) are then compared. In the usual case control study, there is no risk of physical injury since no interventions are performed.

Case-control studies may, however, entail legal risks (for instance, a study may reveal illegal drug use) or psychological risks (for example, the investigation may review traumatic experiences). Principal Investigators should present their plan to protect privacy, assure confidentiality of data and respect the subjects' rights (including refusal to participate).

Case-control studies may require investigators to review medical records and interview subjects, or, when subjects are deceased, their next-of-kin. The IRB will review the study to assure that a suitable system for contacting subjects will be used.

Chart or Medical Record Review

The use of medical records or protected health information (PHI) requires IRB review. Studies which involve only chart /medical record review sometimes pose significant risk to subjects. The most common risk is a breach of confidentiality with the exposure of potentially embarrassing information without the knowledge or consent of the subject. Such studies may also lead to recruitment of subjects into future non-therapeutic studies in a manner which may provoke the subject to ask how his/her record was revealed to someone not part of his/her therapeutic team.

The HIPAA Privacy Rule requires covered entities to obtain each subject's authorization, or an IRB waiver of such authorization, before a researcher (including the subject's treating physician) may access the subject's records or other protected health information for research purposes.

To access charts or medical records for research purposes, the researcher must submit an application to the IRB for approval.

To obtain IRB approval to review medical records at UVa, go to IRB Online and proceed with a new application. This approval is required regardless of where these medical records are located (e.g., Health Information Services-HIS- formerly Medical Records, shadow records in your department, departmental databases, electronic medical record etc.).

In addition, if you need to have charts pulled from HIS, complete the Request for Medical Records Form. Attach a copy of your IRB Approval Form to the Request for Medical Records Form in order to have the charts pulled.

Preparatory to Research or Review of Decedent Information

If the researcher wishes to review charts of decedents, to design a research study or to assess the feasibility of conducting a study, IRB approval is not required, however, the researcher must first complete a Request for Medical Records Form and submit this to the UVa Health System Department of Health Information Services (HIS). In this form the researcher will represent that the use or disclosure of the protected health information is solely to:

- prepare a research protocol or
- for similar purposes preparatory to research,
- that the researcher will not record any protected health information, and
- that protected health information for which access is sought is necessary for the research purpose.

Epidemiologic Studies

Epidemiologic studies present several unique problems because they often use sensitive private documents, such as medical records, and link them with other data, such as employment, insurance or police records. The primary ethical concerns presented by epidemiologic studies are protection of subjects' privacy and the confidentiality of data. Access to those records without prior consent of the subject raises concerns about the violation of the ethical principle of respect for persons (sometimes referred to as autonomy).

The IRB's review is to ensure that epidemiologists take adequate steps to preserve the confidentiality of the data they collect, and that they specify

- who will have access to the data,
- how and at what point in the research personal information will be separated from other data,
- whether the data will be retained at the conclusion of the study, and
- any possible disclosure of the data.

The IRB also requires a thorough description of interview instruments and questionnaires.
When a study involves reviews of records which can be linked to the identity of the subject, the IRB must ensure that subject's privacy interests will be adequately protected and that any uses or disclosures of protected health information for the research comply with any applicable Privacy Rule requirements.
Where the Principal Investigator will have personal contact with subjects, a potential for harm exists since they are identified as potential subjects because they either have or are at risk of developing a disease or condition. Simple contact with subjects may present a risk of harm, either because of sensitivity to discussing a disease or condition they know they have, or because they may not be aware of their condition. Once potential subjects are identified, the Principal Investigator should obtain their consent to participate in the study.
Disclosure of information such as that usually collected in epidemiologic studies also presents an ethical concern. All information collected as part of a study is confidential. Data must be stored in a secure manner and must not be shared inappropriately. The Principal Investigator's protocol should detail how data will be kept and how confidentiality of data will be maintained. Principal Investigators should note, however, that, unlike medical records, research data is not privileged under law unless a Certificate of Confidentiality is obtained and is current.

FDA Requirements for Investigational Drugs, Biologics, and Medical Devices

Research involving drugs, biologics and medical devices is regulated primarily by the Food and Drug Administration (FDA) and provides a transition from promising basic or laboratory research to accepted therapeutic or diagnostic procedures for subjects.

Investigational drug, biologic, and device products (also called “test articles”) include:

- Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA; and
- Products already approved by the FDA as safe and effective for specific indications, that are being studied for new indications, doses, strengths, frequency or vulnerable populations other than those that have been approved.

The Food and Drug Administration (FDA) requires IRB review and informed consent in the same way as NIH or the DHHS (or other Federal agencies that support research). However, the FDA has several additional reporting conditions that involve investigators directly.

Studies of Investigational Drugs or Biologics

Federal law prohibits the distribution of new drugs or biologics until the FDA has reviewed clinical data and determined that a particular product is safe and effective for a specific use in human subjects.

In order to test a new drug or biologic in clinical trials, it is necessary to obtain an exemption from the FDA. Thus a drug sponsor is required to apply for an Investigational New Drug (IND) exemption before tests with human subjects may begin.

In general, the review requirements for biologics are the same as those for drugs. Accordingly, unless otherwise indicated, the provisions that follow use of the term "drug," apply to biologics as well as to drugs. The investigator is responsible for obtaining the IND number and providing it to the IRB. Studies that involve FDA-regulated products that are submitted without a IND number will be reviewed by the IRB with respect to determining the need for an IND, based on federal requirements and the investigator's response to questions contained in the protocol.

If the IRB determines that the study does not require an IND and approves the study, the study may begin. If the IRB determines that an IND is needed, the investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination (IND number) to the IRB before the IRB gives approval to enroll subjects in the study.

Exemption for Drug/Biologics

The IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- The investigation does not involve a route of administration or dosage level or use in a subject population (e.g., children, prisoners, pregnant women and fetuses) or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review and with the requirements for informed consent; and
- The investigation is conducted in compliance with the requirements with regard to promotion

Phases of Studies

The FDA requires various stages of human subject research to ensure that drugs and biologics are both safe and effective for the proposed use. This safety and efficacy data may eventually be used in marketing materials or on the drug's label or subject insert.

Phase One Drug Trials

Phase 1 drug trials include the initial introduction of an investigational new drug into humans. These studies are typically closely monitored and conducted with healthy volunteers; sometimes, where the drug is intended for use in subjects with a particular disease, however, such subjects may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to

obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

Phase Two Drug Trials

Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in subjects with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with relatively small numbers of subjects, usually involving no more than several hundred subjects.

Phase Three Drug Trials

Phase 3 drug trials involve the administration of a new drug to a larger number of subjects in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used in the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand subject-subjects.

Phase Four Drug Trials

Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other subject populations or other stages of the disease, or use of the drug over a longer period of time.

Research concerning new treatments for certain life-threatening conditions (e.g., cancer, AIDS, emergency-room interventions) may progress differently through the four phases. Investigators interested in studying such products should contact the FDA for further information.

Permissible Exceptions for Subject Care

There are several different types of permissible exceptions to a clinical trial for subject care.

- Off-Label Use
- Compassionate Use
- Emergency Use
- Treatment Use
- Expanded Access

Studies of Investigational Medical Devices

Federal law prohibits the distribution of medical devices until the FDA has reviewed clinical data and determined that a particular product is safe and effective for a specific use in human subjects. In order to test a new medical device in clinical trials, it is necessary to obtain an exemption from the FDA. Thus a device sponsor is required to apply for an Investigational Device Exemption (IDE) before tests with human subjects may begin. The investigator is responsible for obtaining the IDE number and providing it to the IRB. Studies that involve FDA-regulated products that are submitted without an IDE number will be reviewed by the IRB with respect to determining the need for an IDE, based on federal requirements and the investigator's response to questions contained in the protocol.

If the IRB determines that the study does not require an IDE and approves the study, the study may begin. If the IRB determines that an IDE is needed, the investigator/sponsor must submit an IDE application to the FDA and provide documentation of the outcome of the FDA determination (IDE number) to the IRB before the IRB gives approval to enroll subjects in the study.

Exemption for Devices

Investigations that are exempted from 21 CFR 812 are described in §812.2(c) of the IDE regulation. A summary of the FDA regulations for studies exempt from the IDE regulation include:

1. a legally marketed device when used in accordance with its labeling
2. a diagnostic device if it complies with the labeling requirements in §809.10(c) and if the testing:
    a. is noninvasive; *
    b. does not require an invasive sampling procedure that presents significant risk;
    c. does not by design or intention introduce energy into a subject; and
    d. is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;

*** Noninvasive** when applied to a diagnostic device or procedure, means one that does not by design or intention:

- Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or
- Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.
- Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.

Additional guidance for an in vitro diagnostic device studies can be found in "Regulating In Vitro Diagnostic Device (IVD) Studies."

3. consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved PMA, cleared Premarket Notification 510(k), or are exempt from 510(k)] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;

4. a device intended solely for veterinary use;

5. a device shipped solely for research with laboratory animals and contains the labeling "CAUTION – Device for investigational use in laboratory animals or other tests that do not involve human subjects."

6. a custom device

   According to 21CFR812.2(c) (7) a custom device as defined in 812.3(b) is exempt unless the device is being used to determine safety or effectiveness for commercial distribution. A custom device means a device that:
   (1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;
   (2) Is not generally available to, or generally used by, other physicians or dentists;
   (3) Is not generally available in finished form for purchase or for dispensing upon prescription;
   (4) Is not offered for commercial distribution through labeling or advertising; and
   (5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.
   Depending upon the nature of the investigation, those studies which are exempt from the requirements of the IDE regulation may or may not be exempt from the requirements for IRB review and approval under Part 56 and the requirements for obtaining informed consent under Part 50. For guidance regarding the applicability of these regulations with respect to investigations being conducted under the provisions of §812.2(c), contact the IDE Staff at (301) 594-1190.

Devices NOT Exempt From FDA Regulations

An unapproved medical device may normally only be used on human subjects through an approved clinical study in which the subjects meet certain criteria and the device is only used in accordance with the approved protocol by a clinical investigator participating in the clinical trial. In order to submit a study for a clinical trial to the IRB-HSR go to Protocol Builder and follow the steps to submit to the IRB-HSR.

Medical Device Definition

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy

Medical Device Classes

In 1976, Medical Device Amendments to the Food, Drug and Cosmetic Act gave the FDA the responsibility for assuring the safety and effectiveness of devices intended for human use. In implementing these Amendments, the FDA has classified devices according to their level of risk.

Class 1 Medical Devices

Class 1 Medical Devices include those devices for which safety and effectiveness can be assured as long as there is compliance with provisions for notification of defects, repair, replacement or refund, records and reports. Device manufacturers are required to also avoid distribution of adulterated, misbranded, or banned devices.

Class 2 Medical Devices

Class 2 Medical Devices are those that require something more than proper labeling and quality assurance to ensure their safety and effectiveness.

Class 3 Medical Devices

Class 3 Medical Devices are those that are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment.

510(K) Devices

When a new device is substantially equivalent to one marketed prior to enactment of the Medical Devices Amendments (1976), it may be sold without additional proof of safety and effectiveness under Section 510(K) of the Federal Food, Drug and Cosmetic Act. These devices are commonly referred to as "510(K) devices." A sponsor planning to market the device must notify the FDA 90 days in advance of placing the device on the market. If the FDA agrees that the device is substantially equivalent to one already on the market, the device may then be sold without further research. Research activities involving a 510(K) device do not require an FDA Investigational Device Exemption (IDE) prior to approval by the IRB.

If the FDA determines that a new device is not substantially equivalent to a pre-amendment device, the new device is automatically designated a Class 3 medical device and the sponsor is required to obtain pre-marketing approval from the FDA. Studies conducted to develop safety and effectiveness data for such devices must be conducted according to the FDA requirements or Investigational Devices.

Significant and Non-Significant Risk Devices

If a device is determined to not be exempt from the IDE regulations- a determination must be made if the device is either significant risk devices or non-significant risk.

Determination of Significant/Non-Significant Risk Status

Sponsors are responsible for making the initial risk assessment regarding an investigational device.

A **non-significant risk device** is one that does not present significant risk to the research subject. Investigators should clearly explain in their protocol to the IRB why the sponsor believes the device to present no significant risk to study participants and provide supporting information, such as reports of prior

investigations. The investigator should inform the IRB whether the FDA or any other IRB (IRB) has made a risk assessment and what the results of those assessments were.

The IRB then will make an independent assessment of the risk of the investigational device to be used in the study. If the IRB agrees that the devices poses no significant risk to research subjects, the investigator will not be required to obtain an IDE from the FDA to conduct the study. If the IRB instead believes that the device poses significant risk to research subjects, the investigator will be notified by the IRB. The investigator in turn is required to notify the sponsor of the IRB's decision, and the sponsor must notify the FDA of the IRB determination regardless of whether the study is ultimately conducted at UVA. Investigational devices determined by the IRB to poses significant risk to research subjects, will be reviewed according to the requirements described below.

Significant Risk Device Criteria

Sponsors are responsible for making an initial risk assessment regarding an investigational device. A significant risk device by definition is an investigational medical device that presents a serious risk to the health and safety of the research subjects. Such a device is:

According to 21CFR812.3(m) a Significant Risk (SR) device study is one that presents a potential for serious risk to the health, safety, or welfare of a subject and

- is intended as an implant*; or
- is used in supporting or sustaining human life; or
- is for use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
- otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Note: If the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure to implant the device, the IRB-HSR must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

***Implant** means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants."

Device Studies in Pediatric Populations

Because the pediatric population represents a particularly vulnerable group, specific measures are needed to protect the safety of pediatric study subjects. Adult devices may be inappropriate for use in pediatric subjects for a variety of reasons, or may require specific design changes and/or specific labeling to accommodate their use in pediatric subjects. We recommend that the researcher consider the following when developing devices or plan a clinical trial for devices intended for pediatric subjects:

- height
- weight
- growth and development

- disease or condition
- hormonal influences
- anatomical and physiological differences from the adult population
- activity and maturity level
- immune status.

If clinical data are needed to support a pediatric indication, the researcher should make every effort to gather data that adequately addresses each targeted pediatric subgroup. In some cases, the expected benefit and safety can be determined without separate studies in each subgroup. That is, it may be extrapolated from one age group to another. In other cases, such as with neonates, clinical data gathered specifically in that subgroup will likely be needed. Please review the FDA publication Premarket Assessment of Pediatric Medical Devices for additional information about research involving pediatric medical devices.

For additional information see the FDA publication Premarket Assessment of Pediatric Medical Devices

Unanticipated Adverse Device Effect Reports

The reporting requirements for adverse device effects are different from those for drugs and biologics. The sponsor-investigator must immediately conduct an evaluation of any unanticipated adverse device effect. If this effect presents an unreasonable risk to subjects, the sponsor-investigator is required to terminate all investigations as soon as possible, but no later than five working days after the sponsor makes this determination. This also must occur within 15 working days of when the sponsor was notified of the adverse effect.

Emergency Use of a Device

For Emergency Use of a Humanitarian Use Device see HUD Emergency Use

Emergency Use of Unapproved Medical Devices

An **unapproved medical device** is a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360(e)].

An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520(g) of the Act [21 U.S.C. 360(j)(g)] and 21 CFR part 812. Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices which require an IDE.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies in writing to the FDA and the IRB that an emergency actually existed.

Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

a. the subject is in a life-threatening condition that needs immediate treatment;
b. no generally acceptable alternative for treating the subject is available; and
c. because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

For additional information see page 10 of Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors : Frequently Asked Questions About Medical Devices

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the FDA Office of Emergency Operations (HFA-615) 301-443-1240.

FDA would expect the physician to follow as many subject protection procedures as possible. These include:

a. obtaining an independent assessment in writing, documented in the subject/subject's medical record by an uninvolved physician;
b. obtaining informed consent from the subject or a legal representative;
c. notifying institutional officials as specified by institutional policies;
d. notifying the Institutional Review Board (IRB); and
e. obtaining authorization from the IDE holder, if an approved IDE for the device exists.

After-Use Procedures

After an unapproved device is used in an emergency, the physician should:

a. report to the IRB within five days [21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [21 CFR part 56];
b. evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
c. if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA

disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing in the subject/subject's medical record all of the following [21 CFR 50.23(a)]:

a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
c. Time is not sufficient to obtain consent from the subject's legal representative.
d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Other Types of IDE's

There may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which there no other alternative therapy exists. Patients/physicians faced with these circumstances may have access to investigational devices under one of four main mechanisms by which FDA may make an unapproved device available:

Compassionate Use

Emergency Use

Treatment Use

Continued Access

Humanitarian Use Devices

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or are manifested in fewer than 4000 individuals in the United States per year. The sponsor must get a HDE designation from the FDA's Office of Orphan Products Development. The Federal Food, Drug, and Cosmetic Act and the HDE regulation do not require informed consent because a HDE provides for marketing approval, and so use of the device does not constitute research or an investigation which would normally require informed consent. The sponsor may provide the patient with patient labeling to assist

the patient in making an informed decision about the use of the device. Even though the device is not considered investigational, IRB review is required. The initial review must by done by full board, although continuations may be done by expedited review. For additional information see:
Humanitarian Use Device
Emergency Use of an HUD

Records Required by the FDA

Protocols conducted according to FDA guidelines must be maintained in accordance with current FDA regulations. Current FDA policy states that investigators are required to maintain records for the longest of either:

- A period of at least two years following the date on which the results of the clinical investigation are submitted to the FDA in support of an application for a r Investigational Device Exemption or marketing permit; or
- A period of at least two years following the date on which an application for research or marketing permit (in support of which the results of the clinical investigation were submitted to the FDA) is approved by the FDA; or
- Two years after the investigation is discontinued and the FDA is notified of that fact.

The FDA regulations include specific instructions for the content of records that must be created and maintained in clinical investigations of devices.

Drug Study Record Requirements

a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under Sec. 312.5947.

b. Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses` notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

c. Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Device Study Record Requirements

Investigator Records for Device Studies

A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

a. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
b. Records of receipt, use or disposition of a device that relate to:
    i. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
    ii. The names of all persons who received, used, or disposed of each device.
    iii. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
c. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
    i. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
    ii. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
d. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
e. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
f. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

Sponsor Records for Device Studies

When the investigator is also a sponsor, the investigator-sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

a. All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.
b. Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

c. Signed investigator agreements including the financial disclosure information required to be collected under 21 812.43(c)(5) in accordance with part 54..

d. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and

e. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

f. IRB records. An IRB shall maintain records in accordance with 21 CFR 56.115.

g. For each investigation subject to 21CFR. 812.2(b)(1) of a device other than a significant risk device, the records described in 21CFR812.(2) (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

i. The name and intended use of the device and the objectives of the investigation;

ii. A brief explanation of why the device is not a significant risk device:

iii. The name and address of each investigator:

iv. The name and address of each IRB that has reviewed the investigation:

v. A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and

vi. Any other information required by FDA.

Required Approval Process to Use a New Device at UVa Health System

No medical device (supplies, accessories, or equipment), whether purchased, contracted, donated, loaned or for trial, may be used in the Medical Center for inpatient or outpatient care purposes without first being evaluated by the Office of Supply Chain Management.

The Food and Drug Administration (FDA) defines a medical device as any instrument, apparatus, or other article that is used to prevent, diagnose, mitigate, or treat a disease or to affect the structure or function of the body, with the exception of drugs. This means that the FDA classifies common hospital products such as catheters, thermometers, patient restraints and syringes as medical devices.

In order to obtain approval submit the completed New Medical Device Monitoring Form to the Office of Supply Chain Management. If there are questions on how to complete the form contact their office at 982-3857. The IRB-HSR will require a copy of the completed New Medical Device Form prior to approving a protocol.

For additional information see the following Hospital Policies:

0076: Medical Devices Evaluation and Monitoring System

#0165: Safe Medical Devices Act Reporting

Investigators as Sponsors

If an investigator is the developer of the drug, biologic or medical device, and no commercial manufacturer is involved, then the investigator is also the sponsor for the purposes of designing and organizing clinical trials.

- When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an Investigational New Drug (IND) or Investigational Device Exemption (IDE) may be required. If an IND or an IDE is required, it is the investigator's responsibility to submit

the appropriate application to the FDA, obtain the necessary documentation, and provide this documentation to the IRB as a part of the approval process.

- An IND may not be necessary if all of the conditions stated in 21 CFR 312.2(b)(1) have been met. If the PI does not already have an IND, the PI will be notified in writing that IRB approval is pending receipt of an IND. If there is a debate regarding the need for an IND, the IRB will require that the PI contact the Food and Drug Administration (FDA) to obtain written documentation that an IND is not necessary.
- The IRB will review protocols involving investigational devices to determine if the device is exempt from IDE regulations. If not exempt, the IRB will then determine if the device is a "Significant-Risk device" (SR) or a "Non-Significant Risk"(NSR) device. If the IRB determines that the research involves a SR device, an IDE is necessary. If the PI does not already have an IDE, the PI will be notified in writing that IRB approval is pending receipt of an IDE.

Sponsors also have important administrative and reporting requirements above and beyond those of investigators. Faculty contemplating the dual role of sponsor-investigator should consult with the School of Medicine Clinical Trials Office (SOM CTO) about the additional responsibilities that entails.

The sponsor must declare any individual financial conflict(s) of interests in the research and develop a management plan that is approved by the University.

Multi site trials:

Should an investigator associated with the University of Virginia or the University sponsor a multi-site study, that investigator is required to meet all the responsibilities of a sponsor as determined by DHHS guidance.

A common protocol is required for all multi-site trials. See Multi-Site Studies for additional information. At the time of initial review the IRB will require an approval from the SOM CTO who will assess the procedures for dissemination of protocol information (e.g. unanticipated problems involving risks to subjects or others, protocol modifications, interim findings) to all participating sites. In addition the UVA PI must ensure that investigators at other research sites submit and follow requirements directed by their local IRBs.

IRB policies and procedures from each approving institution will be followed by researchers at that site. All required reports will be provided to the local IRB as per their policy. The coordinating PI at the University of Virginia will be responsible for providing local information as well as unanticipated problems involving risks to subjects or others, protocol modifications, or interim findings that may affect the UVA IRB's continuing approval of the research.

The IND or IDE application must contain sufficient data from animal and in vitro studies to demonstrate the likelihood that the product will be safe and effective for the purpose indicated. If the FDA agrees that the data are sufficient to support a decision to initiate clinical trials, and the proposed protocol is acceptable, the FDA will provide an IND or IDE number to the protocol. Specific requirements for protocol design are set forth in FDA Regulations.

IDE: The investigator is required to wait for the FDA scientists to review the materials submitted, and if necessary request additional information, require modifications, and approve or disapprove the application before proceeding with the clinical trial. The IRB will not provide approval to enroll subjects in the study until the FDA has either provided an IDE number or advised the principal investigator that an IDE is not required.

IND: The investigator is required to wait 30 days after submitting the IND application to the FDA before enrolling subjects. During this time the FDA scientists will review the materials submitted, and if necessary request additional information or require modifications. The FDA may send the sponsor an IND #, however

this is not an approval to proceed. The IRB will not provide approval to enroll subjects in the study until the 30 day time period has passed.

If a UVA faculty member is the principal investigator on an IND or IDE, the IRB-HSR will require an approval from the School of Medicine Clinical Trials Office prior to subjects enrolling in the protocol. Prior to granting approval, the SOM CTO will conduct of review of various items with special focus on areas of FDA interest such as- inclusion/exclusion criteria, safety plan , endpoints, data collection process and the communication plan with other sites , if multi-site. The staff of the SOM CTO will also review Sponsor responsibilities with the PI. Sponsor responsibilities for an IND are found at 21CFR312. Sponsor responsibilities for an IDE are found at 21CFR812

Human Embryonic Stem Cell Research

Background

Embryonic stem cells. Embryonic stem cells, which come from the inner cell mass of a human embryo, have the potential to develop into all or nearly all of the tissues in the body. The scientific term for this characteristic is "pluripotentiality."

Adult stem cells. Adult stem cells are unspecialized, can renew themselves, and can become specialized to yield all of the cell types of the tissue from which they originate. Although scientists believe that some adult stem cells from one tissue can develop into cells of another tissue, no adult stem cell has been shown in culture to be pluripotent.

The potential of embryonic stem cell research. Many scientists believe that embryonic stem cell research may eventually lead to therapies that could be used to treat diseases that afflict approximately 128 million Americans. Treatments may include replacing destroyed dopamine-secreting neurons in a Parkinson's patient's brain; transplanting insulin-producing pancreatic beta cells in diabetic patients; and infusing cardiac muscle cells in a heart damaged by myocardial infarction. Embryonic stem cells may also be used to understand basic biology and to evaluate the safety and efficacy of new medicines.

The creation of embryonic stem cells. To create embryonic stem cells for research, a "stem cell line" must be created from the inner cell mass of a week-old embryo. If they are cultured properly, embryonic stem cells can grow and divide indefinitely. A stem cell line is a mass of cells descended from the original, sharing its genetic characteristics. Batches of cells can then be separated from the cell line and distributed to researchers.

The origin of embryonic stem cells. Embryonic stem cells are derived from excess embryos created in the course of infertility treatment. As a result of standard in vitro fertilization practices, many excess human embryos are created. Participants in IVF treatment must ultimately decide the disposition of these excess embryos, and many individuals have donated their excess embryos for research purposes.

Additional Information

Genetic Research

Federal guidelines strongly advise IRBs to consider specific issues when reviewing clinical genetic research and to alert investigators engaged in such research to address these issues in their application for IRB approval. Unlike the risks presented by biomedical research, the primary risks of genetic research are risks of social and psychological harm rather than risks of physical injury. Genetic studies that generate information about

subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise subjects' insurability and employment opportunities. Although these genetic studies may be limited to a collection of family histories or blood draws, the IRB does not necessarily consider them to be minimal risk.

What qualifies as genetic research?
Genetic research does not mean only research that involves looking for mutations in DNA. Research that involves looking at the differences between proteins in individuals with or without a certain disease can also qualify as genetic research. Records research involving information that was derived from a previous genetic test can also qualify as genetic research. See definitions below.

- **Genetic research**: Research using human DNA samples, genetic research or genetic information.
- **Genetic information**: Information about an individual or the individual's blood relatives obtained from a genetic test.
- **Genetic test**: A test for determining the presence or absence of genetic characteristics in a human individual or the individual's blood relatives, including tests of nucleic acids, such as DNA, RNA, and mitochondrial DNA, chromosomes or proteins in order to diagnose or determine a genetic characteristic.
- **Genetic characteristic**: A gene, chromosome or alteration thereof that may be tested to determine the existence of or risk for acquiring a disease, disorder, trait, propensity or syndrome, or to identify an individual or a blood relative. "Genetic characteristic" does not include family history or a genetically transmitted characteristic whose existence or identity is determined by means other than through a genetic test.
- Genetic Research FAQs

Disclosure of Research Results to Subjects

Disclosure of genetic research findings to a research subject or the subject's physician through use of personal identifiers should not occur unless:

i. The research findings are scientifically valid and confirmed (done in a CLIA approved lab);

ii. The findings have significant implications for the subject's or the public's health; and

iii. A course of action to ameliorate or treat the subject's or the public's health concerns is readily available.

IRB approval is required before disclosure of research results can occur. In the event these conditions are met, the results may only be released to the subject or any other party with the subject's permission, and appropriate medical advice and referral must be provided.

Re-contact of a research subject or a patient from whom samples or information was obtained originally for clinical purposes should not occur unless the subject was informed during the initial treatment or research consent and authorization process, that re-contact may occur under specified circumstances. Reasons for re-contacting research subjects can include re-contact for release of clinically relevant research results. If this is desired, precautions must be taken both to minimize the potential harm to subjects of receiving bad news and to guard against the unintended release of the information. The precautions needed in conveying genetic research results depend on the age at onset of the disorder, the burden of illness, and the availability of treatment or prevention. The communication of genetic information carries with it the responsibility to interpret the results

and provide care for the individual; and, thus, it is ideally done in the setting of a clinical rather than research relationship with the subject. Because of the complexity of the results of most genetic tests, subjects cannot be required to inform relatives of the results of the research

Retaining Samples, Specimen Banks
Whether or not an activity qualifies as specimen banking depends on the researcher's intent. Here are some examples:

- If extra blood is drawn and stored as a back-up in case a test to which research subjects have already consented needs to be repeated, but once the test results are in the extra samples are destroyed, this is not specimen banking even though tissue samples are stored.
- However, if the researcher wants to collect extra samples in case they want to do additional analysis later on that was not included in the original, IRB-approved protocol, that is specimen banking and the researcher must get IRB approval and subject consent to do so. After the additional test has been conducted, the sample should be destroyed, unless the subject has consented otherwise.
- If the researcher wants to collect extra samples to keep on hand for other investigators to use or for use in another study, that is specimen banking.
- If the researcher has samples stored in case tests need to be repeated, but then decide they would like to perform an additional test (based on interesting preliminary results, for example), the researcher must get IRB approval and subject consent to do so. After the additional test has been conducted, the sample should be destroyed, unless the subject has consented otherwise.

The basic rule is this: if the researcher is storing tissue for any additional uses not specified in the consent form signed by the research subject and approved by the IRB, they are banking tissue.

Genome Wide Association Studies (GWAS)

Background
A GWAS study is any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. Whole genome information, when combined with clinical and other phenotype data, offers the potential for:

- increased understanding of basic biological processes affecting human health,
- improvement in the prediction of disease and patient care, and
- ultimately the realization of the promise of personalized medicine.

The NIH Policy for Genome Wide Association Studies (GWAS) applies to protocols for which the NIH will cover the cost of the GWAS analysis via a grant or contract that was submitted for NIH funding after January 25, 2008.

Competing GWAS applications to NIH must include a GWAS data sharing plan as part of the research plan or outline why such data sharing is not appropriate.

Data Sharing Plan:

The data sharing plan of the research plan (grant application) should include:

- Documentation that the data submission is consistent with applicable federal and Virginia laws and institutional policies
- The appropriate research uses of the data and any specific research exclusions per the intent of the study and as outlined in the informed consent document
- *If samples have not yet been collected* the informed consent document should include information regarding the data sharing. The informed consent must be clear that DNA will undergo genome-wide analysis and that genotype and phenotype will be shared for research purposes with investigators who submit proposals to the GWAS data repository. (The IRB-HSR consent form template contains suggested language for use).
- *If samples have already been collected* the IRB must review the informed consent documents which were signed by participants to confirm whether or not the initial consent under which genetic materials were obtained is consistent with the submission of data to the GWAS data repository and the sharing as outlined in the GWAS policy.
    - The IRB may determine that the original consent is not inconsistent with the submission of data to the GWAS data repository and provide certification as documentation.
    - The IRB may determine that the original consent is not consistent with submission of data to the GWAS data repository and may request re-consent of subjects.
    - The IRB may determine that the original consent is not consistent with submission of data to the GWAS data repository and determine that it cannot verify that the criteria outlined in the GWAS policy have been met for submission of data to the GWAS data repository and therefore, such submission is not appropriate.

Submission of Data To dbGaP: Institutional Certification

Background:

All submissions to the NIH GWAS **D**ata**b**ase of **G**enotypes **a**nd **P**hentotypes (dbGaP) of data should be accompanied by a certification by the responsible Institutional Official(s) of the submitting institution that they approve submission to the NIH GWAS data repository.

In order to determine if a certificate may be given, the PI will need to submit to the IRB the consent form templates under which the original specimens were collected. If the consent version changed over time, the IRB will need to see all versions of the consent used.

The certification should assure that:

- The proposed data submission is consistent with applicable federal and Virginia laws and regulations, as well as institutional policies ;
- The research uses of the data and the uses that are specifically excluded by the intent of the study and the informed consent documents are described.
- The proposal provides that the identities of research participants will not be disclosed to the NIH GWAS data repository; and
- The institution's IRB for Health Sciences Research (IRB-HSR)/ Privacy Board has reviewed the relevant aspects of the proposal and verified that
  - The proposed submission of data to the general NIH GWAS data repository for subsequent sharing for research purposes as described in the NIH Policy is not inconsistent with the intent of the study and the informed consent of study participants from whom the data were obtained;
  - The investigator's plan for de-identifying datasets is consistent with the NIH "Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies"
  - Based on the characteristics of the subject population and the data involved in the primary study, and within the limits of its knowledge of the future potential uses and users of the data, it has considered the risks to individuals, their families, and groups or populations associated with the proposed submission of the data to the general NIH GWAS data repository. The IRB/Privacy Board understand that assessment of risks associated with specific future secondary uses will be performed by NIH's Data Access Committees, and,
  - To the extent applicable, the genotype and phenotype data proposed to be submitted were collected/will be collected in a manner consistent with 45 C.F.R. Part 46.

Privacy Protections:

Due to the potentially sensitive nature of the data, steps must be taken to protect the privacy of the individual data.

- De-identification or Coding of Data: Before data are submitted to the NIH GWAS dbGaP, submitting investigators will be expected to de-identify the data per HIPAA regulations or assign a random, unique code to the data to protect the subjects privacy and confidentiality.
- The key to the code will remain at UVa and will never be shared with GWAS.
- This information must be stipulated in the protocol.

Withdrawal of Individual Consent:

The NIH GWAS data repository has developed policies with regard to removal of individual data records if consent is withdrawn. Submitting investigators and their institutions may request removal of coded data on individual participants from the data repository in the event that a research participant withdraws consent. However, data that have already been distributed for approved research use will not be able to be retrieved.

Procedure:

If you do not already have IRB approval to receive/ collect the data /specimens see Receipt of Data/ Specimens to determine type of IRB approval required.

If UVa holds NIH grant application:

- Review Sending Data/ Specimens to determine what type or IRB approvals are required.
- The IRB-HSR will review the NIH grant application when submitted to the IRB. The IRB-HSR Grant Information form includes information the IRB-HSR needs to process the request for an institutional certification to deposit data into dbGaP.
- In order to determine if a certificate may be given, the PI will need to submit to the IRB the consent form templates under which the original specimens were collected. If the consent version changed over time, the IRB will need to see all versions of the consent used.
- The IRB-HSR will work with the Office of the VP for Research to determine the applicability of the certification.
- If certification is granted, the document will be given back to the PI of the Grant Proposal Application along with the IRB-HSR approval of the grant.

If UVa DOES NOT hold an NIH grant application:

- Review Sending Data/ Specimens to determine what type or IRB approvals are required.
- Submit a dbGaP Submission Certification Request Form to the IRB-HSR
- In order to determine if a certificate may be given, the PI will need to submit to the IRB the consent form templates under which the original specimens were collected. If the consent version changed over time, the IRB will need to see all versions of the consent used.

Use of Data from dbGaP

Background:

The dbGaP has two levels of access:

- The Open-Access Data contains the study information deposited as required under the GWAS Policy. The Open-Access portion of the dbGaP may be browsed online or downloaded from the dbGaP without prior permission or authorization.
- The Controlled-Access portion of the dbGaP contains individual-level information that may only be obtained if a user has been authorized by the appropriate NIH Data Access Committee.

The IRB-HSR does not generally consider the access and use of either open-access data or controlled access data to meet the definition of human subjects' research. Therefore, IRB review of the researcher's plans for using such data is not required. This is based on Office for Human Research Protections (OHRP) advisement to NIH that the dbGaP does not currently involve human subjects' research because the data will be coded and the

identity of individuals with whom the data were obtained will not be readily ascertainable to the investigators maintaining the repository.

Some controlled-access datasets have restrictions on the use of the data and may require IRB review and approval prior to their release to the requesting researcher. This information is outlined in the Data Use Certification document located on the GWAS website.

The NIH document " Points to consider for IRBs and Institutions" provides the following information regarding this certification.

Investigators and institutions seeking data from the NIH GWAS data repository will submit to the NIH a Data Access Request along with a Data Use Certification that will stipulate a number of protections for research participants. Both the Data Access Request and the Data Use Certification must be co-signed by the investigator and by the appropriate designated Institutional Official to document their joint agreement to follow NIH policy for the use of GWAS data obtained from the NIH GWAS data repository. The Data Use Certification will stipulate that, subject to applicable law, the investigator and institution will:

- *Use the data only for the approved research;*
- *Protect data confidentiality;*
- *Follow appropriate data security protections;*
- *Follow all applicable laws, regulations and local institutional policies and procedures for handling GWAS data;*
- *Not attempt to identify individual participants from whom data within a dataset were obtained;*
- *Not sell any of the data elements from datasets obtained from the NIH GWAS data repository;*
- *Not share with individuals other than those listed in the request any of the data elements from data sets obtained from the NIH GWAS data repository;*
- *Agree to the listing of a summary of approved research uses within the NIH GWAS data repository along with his or her name and organizational affiliation;*
- *Agree to report violations of the GWAS policy to the appropriate DAC;*
- *Acknowledge the GWAS policy with regard to publication and intellectual property; and*
- *Provide annual progress reports on research using the GWAS dataset.*

> *The recipient investigator will be expected to protect the data by following best practices for data security posted on the NIH GWAS data repository website at http://www.ncbi.nlm.nih.gov/projects/gap/pdf/dbgap_2b_security_procedures.pdf, or other dataset-specific recommendations as detailed for a given GWAS within the repository. In addition, progress reports will be reviewed by the relevant DAC to verify continued appropriate use of the data.*

For more detailed instructions, refer to the dbGaP request procedures to access individual-level data available at: http://dbgap.ncbi.nlm.nih.gov/aa/dbgap_request_process.pdf

Procedure:

- To determine the type of IRB application required see Receipt of Data/ Specimens.

- To obtain an Institutional Certification submit a signed dbGaP Data Use Certification Form to the IRB-HSR.
- If you have additional questions, contact the IRB-HSR Director at 434-924-9634.

Additional Information/Resources

Additional information may be found on the NIH GWAS website and specifically under:

- National Institute of Health (NIH) Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)
- GWAS NIH Points to Consider for IRB's and Institutions in their Review of Data Submission Plans for Institutional Certification.
- GWAS Tips for Informed Consent for Genomic Research

"GINA" The Genetic Information Nondiscrimination Act of 2008: Information for Researchers and Health Care Professionals

Human Gene Transfer Research

The following explanations are provided to assist investigators in determining whether their proposed research may constitute human gene transfer and, therefore, require additional oversight.

What is DNA?

Deoxyribonucleic acid (DNA) is the building block of life. This molecule encodes different characteristics in all living things. With the exception of identical twins, all individuals have different DNA molecules. In some individuals, the DNA contains mutations that encode aberrant messages. These mutations can cause abnormalities that may result in disease.

What is not Human Gene Transfer Research?

When DNA is manipulated outside of the body but is not integrated into a person's genome, it is an example of recombinant DNA (rDNA) research but is not gene transfer. Likewise, if protein or RNA products of the rDNA are injected into a person, no gene transfer has occurred.*

Experiments involving rDNA require review and approval by the UVa Institutional Biosafety Committee (IBC). Institutional Review Board (IRB) review and approval is required if human subjects are involved. Institutional Animal Care and Use Committee (IACUC) review and approval is required if vertebrate animals are used.

*Note: use of retroviral vectors constitutes human gene transfer.

What is Human Gene Transfer (a.k.a. "Gene Therapy")?

Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. DNA may be transferred as "naked" DNA, encapsulated DNA, or DNA within another organism, such as a virus. Use of

retroviral vectors in humans also constitutes human gene transfer when the virus contains enzymes that result in a DNA copy of the RNA genome.

Human gene transfer is experimental and is being studied to see whether it could treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease. Human gene transfer may help improve genetic disorders, particularly those conditions that result from inborn errors in a single gene (for example, sickle cell anemia, hemophilia, and cystic fibrosis). It may also hold promise for diseases with more complex origins, like cancer and heart disease. Gene transfer is also being studied as a possible treatment for certain infectious diseases, such as AIDS. This type of experimentation is sometimes called "gene therapy" research.

Scientists are attempting to determine whether human gene transfer can be safe and effective as a treatment for disease. Some experimental gene transfer procedures involve the introduction of DNA into cells, which then are injected into a person with disease. All such human gene transfer research studies require approval by the Institutional Review Board (IRB-HSR), the UVa Institutional Biosafety Committee (IBC), and the NIH Recombinant DNA Advisory Committee (RAC).

Federal Oversight and Review Requirements

Human Gene Transfer Research is defined by federal regulations as, "Any deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA (technology), into human research participants."

The NIH Office of Biotechnology Activities (OBA) exists because human gene transfer research raises scientific, medical, ethical, and social considerations worthy of special attention and public discussion. Some of these issues arise from the fact that the techniques being used are relatively new and their risks and benefits are not well characterized.

The NIH OBA review process allows for an in-depth examination of the issues associated with this technology in a setting where public input and comment is encouraged. This open discussion has two important benefits:

- It disseminates this information to scientists who can then incorporate new scientific findings and ethical considerations into the design of trials they may be conducting or planning. The efficiency of the research system is improved by allowing scientists to build on a common foundation of new knowledge emanating from this ongoing process of analysis and assessment.
- It creates enhanced public awareness and allows for a public voice in the review of the safety and ethics of gene transfer research. This helps assure the public that scientists are attending to these important matters and sustains confidence in the enterprise.

The Recombinant DNA Advisory Committee (RAC)

The RAC is a panel of national experts in various fields various fields of science, medicine, genetics, ethics, and patient perspectives that considers the current state of knowledge and technology regarding recombinant DNA research. A key role of the RAC is to advise the NIH Director and the NIH Office of Biotechnology Activities (OBA), which is the NIH locus of oversight for recombinant DNA research. In this capacity, the RAC recommends changes to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), which outline responsible research practices in basic and clinical recombinant DNA research.

Another important RAC function is to review research proposals involving human gene transfer research, or "gene therapy" as it is often called. All human gene transfer trials occurring at or sponsored by institutions receiving NIH funds for recombinant DNA research must be submitted to OBA for review by the RAC.

To learn more about the RAC, please visit the OBA website.

Who is Responsible for the RAC Submission?

See the RAC website for an overview of the submission process.

- For **UVa investigator initiated studies** (i.e., the production of vectors for human application is performed by the UVa investigator), the UVa investigator is responsible for the submission of the relevant information on the proposed human gene transfer experiments to NIH Office of Biotechnology Activities (OBA) in accordance with Appendix M of the NIH Guidelines.
- For **Sponsor initiated studies** (i.e., the production of vectors for human application is not performed by the UVa investigator) the Sponsor must complete the RAC submission process and provide the UVa investigator with the required Appendix M information for the IBC review

UVa School of Medicine Gene Transfer Policy

In addition to following IRB policies investigators must follow the School of Medicine Gene Transfer Policy.

Multi-Site Studies

If a study will be conducted at multiple sites, the IRB-HSR requires a common protocol that is used by all sites. A common protocol is required even if the overall PI is not from UVa. If a common protocol does not exist, templates for a common protocol may be found on the IRB-HSR Website at http://www.virginia.edu/vpr/irb/hsr/writingassistance.html may be used. Templates exist for different types of studies such as a minimal risk study requiring expedited review, a study with more than minimal risk requiring full board review. Templates are also available for studies involving an investigational drug, device or biologic.

In addition, if the protocol requires full board review, the protocol must also be submitted to the School of Medicine Clinical Trials office for their review.

Placebo Controlled Studies

Background

The use of a placebo in clinical research continues to be a topic of debate in the medical community. Some argue that use of placebos is often unethical because alternative study designs would produce similar results with less risk to individual research participants. Others argue that the use of placebos is essential to the protect society from the harm that could result from the widespread use of ineffective medical treatments.

Per the OHRP guidebook, "Placebos may be used in clinical trials where there is no known or available (i.e., FDA-approved) alternative therapy that can be tolerated by subjects." The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and subjects must be fully informed of the risks involved in assignment to the placebo group. Continued assignment of subjects to placebo is unethical once there is good evidence to support the efficacy of the trial therapy. Some drug trials involve a period during which all participants receive only a placebo prior to the initiation of the study. This period is called a placebo washout. The purposes of a washout period include:

- terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug - and only the trial drug - may be observed;
- learning whether subjects cooperate with instructions to take drugs; and
- learning which subjects are "placebo responders," in that they experience a high degree of placebo effect.

In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo. The risks entailed in withdrawing subjects from therapy during a placebo washout period will be carefully evaluated by the IRB; great care must be taken to exclude subjects who are vulnerable to harm or injury if they are withdrawn from effective therapy. In studies involving a placebo washout, subjects must be told that at some point during the study all subjects will receive placebo treatment (OHRP Guidebook).

Protocol and Consent Suggestions for Use of Placebo

Researchers should include the following information in the protocol:

- justify the use of the placebo,
- compare the use of placebo to standard therapy, and
- outline the methodology that will be used to minimize risks to subjects.
- If vulnerable populations are included in the study, the investigator must discuss and justify their participation and detail how subjects will be adequately protected.

The following are methods that can be used to minimize risks associated with the use of placebo:

- Exclude subjects with an increased risk of harm from non-response.
- Include in the protocol increased monitoring for subject deterioration and the use of rescue medications.
- "Early escape" mechanisms and explicit withdrawal criteria may be built in so subjects will not undergo prolonged placebo treatment if they are not doing well.
- The size of the population placed on placebo may be smaller than the number in active treatment arms.
- Placebo and active treatment may be compared in an "add-on" method, keeping the subjects on identical maintenance treatments and then adding on the active treatment to one arm and placebo to the other. This design is especially applicable when the available treatment is known to decrease mortality or morbidity.
- Shortened treatment periods reduce the risks associated with delayed treatment. In situations in which long-term placebo treatment would not be acceptable, the use of a placebo group for a short period at the beginning of a trial could establish short-term effects. The trial would then continue without the placebo group.
- Unblinded data review by a Data Safety Monitoring Board with interim analysis of study results and safety issues. This is especially important for multi-center site studies.

If a placebo is used in a study, the informed consent form should include all of the following information:

- Subjects must be informed that they may be given a placebo.
- A clear lay definition of the term "placebo."
- The rationale for using a placebo must be explained to the subjects.
- If applicable, subjects must be informed of any viable medical alternatives to being placed on placebo.

- The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained.
- Any consequences of delayed active treatment must be explained to the subjects.
- A statement in the Risk section of the consent that the subject's condition may worsen while on placebo.
- A discussion in the Benefits section that subjects who receive placebo may not receive the same benefit as those who receive active treatment if that treatment is effective.

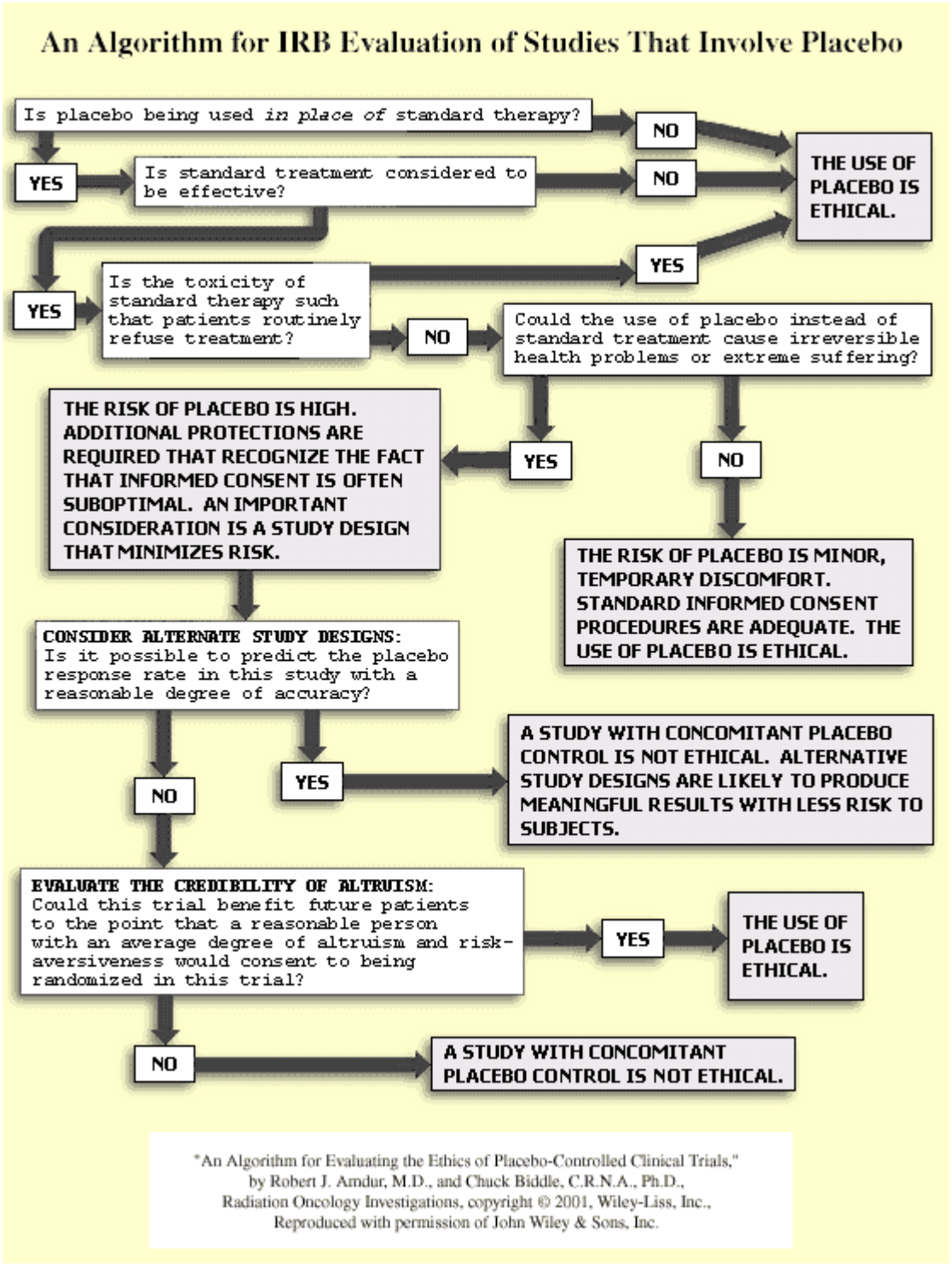
Protocol and Consent Form Suggestions for Placebo Washout Periods

Studies that involve washout periods (with or without the use of a placebo) present similar concerns about risk to subjects as studies using placebos because both involve withholding available therapy from subjects. Therefore, similar attention should be paid to justification of the use of a washout period including methods to minimize risks to subjects. Researchers should include the following information in the protocol:

- the reason why active therapy is being withheld,
- the duration of the washout period,
- the risks specific to this phase of the study,
- increased subject monitoring during the washout period, and
- instructions to the subjects about what to do if they experience problems while off active treatment.
- Use of a washout period, possible risks to the subject, and methodology to address problems that may occur during the washout period must be included in the consent form.

Algorithm of IRB Evaluation of Studies Involving Placebo

The decision algorithm below will help researchers and IRBs evaluate the ethics of using a placebo-control arm in a clinical research trial.



"An Algorithm for Evaluating the Ethics of Placebo-Controlled Clinical Trials," by Robert J. Amdur, M.D., and Chuck Biddle, C.R.N.A., Ph.D., Radiation Oncology Investigations, copyright © 2001, Wiley-Liss, Inc., Reproduced with permission of John Wiley & Sons, Inc.

Radiation Exposure for Research Purposes

Certain types of protocols involve the use of a radiology device or radioactive material in a research-only setting (no clinical care is implied).In these situations the Radiation Safety Committee (RSC) and the IRB will assess

the level of radiation exposure more carefully. The IBC and the IRB require the inclusion of specific information regarding the risks of the radiation exposure in the consent form.

When reviewing a protocol involving the administration of a radioactive material to human subjects for research purposes, the IRB determines whether the research is performed in a manner that protects the rights and welfare of the human subjects by conducting a risk/benefit analysis of the study. The RSC reviews the science of the radiation dose to be absorbed by the subject during research participation.

IRB/ RSC Requirements

If a protocol involves the administration of a radioactive material for research purposes, the IRB requires written approval from the RSC if the investigator does not use standard wording approved by the RSC. The protocol may be submitted to the IRB and the RSC simultaneously, however, the IRB will not give approval to enroll subjects until they receive the RSC approval.

Use of Radiology Devices and Radioactive Materials in Human Subjects

When reviewing a protocol involving the administration of a radioactive material to human subjects for research purposes, the IRB determines whether the research is performed in a manner that protects the rights and welfare of the human subjects by conducting a risk/benefit analysis of the study. The RSC reviews the science of the radiation dose to be absorbed by the subject during research participation.

Positron Emission Tomography (PET)

Investigators using PET radio-pharmaceuticals have the same review requirements as researchers using other radioactive radio-pharmaceuticals. If the research is conducted under an IND, under a treatment IND, or as research on an approved drug for a new indication, then prospective IRB review and approval is required. Prospective IRB review and approval is also required for research using radio-pharmaceuticals to study human physiology, pathophysiology, or biochemistry.

FDA Requirements for the Use of Radioactive Materials in Research

The FDA requires investigators/sponsors to submit an IND for radioactive drugs, biologics, and/or "cold" kits to be used for radio labeling, and radionuclide generators that are used for investigational purposes, including testing their safety and effectiveness. An IND is not required for research designed to study basic biochemistry, physiology, pathophysiology, or metabolism when it is reviewed and approved by the RSC and the IRB. Review and approval by the RSC and IRB of such studies is in lieu of obtaining FDA review and approval of an IND.

The IRB is required to review research according to FDA regulations pertaining to the protection of human subjects. The FDA regulates various aspects of the use of radiology, including quality control, certification of facilities, and approval of radiologic drugs and devices. The study design is required to meet specific FDA requirements. Subjects may not be treated with an investigational form of radiation or radiopharmaceutical unless they are enrolled in an IRB reviewed and approved study with an IRB reviewed and approved informed consent.

Randomized Trials

Randomized clinical trials present numerous ethical issues. A randomized controlled design may be justified where there is a current or likely dispute among expert members of the clinical community as to which of two or more therapies is superior in all relevant respects. The control treatment must be the best standard therapy currently available for the condition being treated. Principal Investigators should discuss how subjects will be assigned to the different groups and who will know which subjects are assigned to each group.

Scientific Review

UVA policy and federal regulations require that the IRB determine whether the risks to subjects are minimized and are reasonable in relation to the importance of the knowledge that may reasonably be expected to result. The IRB has determined that it is inappropriate to place a subject at risk (or inconvenience) in a study where the science and/or research design is so flawed as to preclude development of any reliable information.

Surveys / Questionnaires / Interviews

Surveys, questionnaires and interviews are commonly used in social science disciplines as well as psychology, psychiatry, nursing, and sociology. The IRB may determine that research involving a survey or interview with adult subjects is exempt from IRB review and informed consent. Survey and interview research involving children may not be exempted from IRB review. Principal Investigators must submit to the IRB the texts of interview and/or survey instruments.

Specimen Collection, Use of Existing Specimens/Data and Subject Specific Registries,

A great deal of contemporary research is dependent on the ready accessibility of personally identifiable, *i.e.*, linkable, archival subject materials, such as medical records and specimens removed in the course of routine medical care. In many studies the Principal Investigator must have the ability to obtain follow-up information about particular sets of subjects in order to evaluate the significance of findings and interpret them in an appropriate biological, clinical or epidemiological context. Such studies require that archival subject materials be coded in such a way that they remain permanently linkable to specific subjects. Such studies require that the IRB and Principal Investigators address issues of privacy, confidentiality and informed consent.

Washout

The purposes of a therapeutic washout period with or without a placebo include: (1) terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug, and only the trial drug, may be observed; (2) learning whether subjects cooperate with instructions to take drugs ("compliance"); and (3) learning which subjects are "placebo responders".
The risks entailed in withdrawing subjects from therapy during a washout period with or without placebo are carefully evaluated by the IRB. Such protocols must detail how the research team will monitor subjects for adverse events and the clinical indicators which would lead the investigator to end a washout or placebo period.

SPECIAL CONSIDERATION FOR PROJECTS INVOLVING VULNERABLE POPULATIONS

There are a number of research populations described in the Federal regulations as "vulnerable" or that require additional consideration or protection. "Vulnerable" or "special" classes of subjects include:

- pregnant women,
- human fetuses and neonates,
- prisoners,
- children,
- cognitively impaired persons
- economically and/or educationally disadvantaged.

In addition, the regulations outline specific provisions for research involving:

- fetuses,
- pregnant women, and in vitro fertilization
- prisoners, and
- children.

In reviewing these research projects, the IRB determines that the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population.

Vulnerable Subjects and Exempt Research

Due to the vulnerable nature of the population the exemptions in 45 CFR 46.101(b) do not apply to certain types of research involving children and prisoners, Subparts C and D.

Specifically, the exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

In addition, exemption from IRB review should be utilized conservatively when applied to research involving special classes of subjects who are not be defined by regulation as vulnerable.

The following section is a brief discussion regarding the "vulnerable" subject populations.

In reviewing these research projects, the IRB determines if the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population.

During it's review the IRB must determine which of the following categories the research would involve:

- the research does not involve more than minimal risk to the subject;
- the research is likely to benefit the subject directly, even if the risks are considered to be more than minimal;
- the research involves greater than minimal risk with no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition; or
- research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the subject.

Requests for approval of any research that exposes vulnerable populations to risks that do not meet one of the above criteria must be submitted to the United States Secretary of Health and Human Services for review and approval.

Special protections are essential to guide research involving vulnerable persons. In order to review projects involving the use of vulnerable populations as specified in 45CFR46, an IRB must have present at its meeting an advocate for these subjects.

> The mere presence of the appearance of vulnerability should not lead to a presumption that a person is incapable of making a decision regarding participation in research and of giving valid informed consent. Yet sometimes these conditions do impair the decision-making capacity required to give a valid informed consent, raising ethical concerns about the vulnerability of persons in such conditions in research.

CHILDREN

The legal mandate of the IRB is to protect the rights and welfare of human subjects. This task becomes more difficult when considering children as research subjects. OHRP provides an FAQ on this topic. The Federal regulations provide for "Additional Protections for Children Involved as Subjects of Research." Subpart D of 45 CFR 46. "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (45CFR46.402(a). In the state of Virginia the legal age is 18 however some exceptions may apply.

The definition of "children" also takes into account the particular treatments or procedures involved in the proposed research; for example, in some places individuals who are sixteen years of age may legally consent to certain medical treatments, and so if the involvement of human subjects in a proposed research activity consists of these treatments, then they may be considered as adults for that purpose. If a proposed activity includes something for which the subject has not yet reached the legal age of consent, however, that person must be considered a child.

An FAQ from OHRP states

> *Question*
>
> *If by law a child is able to consent to treatment without parental permission, can they also consent to participate in research related to that treatment?*
>
> *Answer:*
>
> *HHS regulations at 45 CFR 46.402(a) define "children" as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." If research on a specific treatment involves solely treatments or procedures for which minors can give consent outside the research context (under applicable state and local laws, for example, research on sexually transmitted diseases or pregnancy), such individuals would not meet the definition of children as defined at 45 CFR 46.402(a). Thus, subpart D would not apply to the research and parental permission (or waiver thereof) is not a consideration for these minors. Under these circumstances, minors may provide their own informed consent.*

Issues to consider when proposing to involve children in research

- Is the participation of children as research subjects justified in this particular instance?
- If this research question can be addressed initially in adults, has this research been conducted?
- Have results from any adult research indicated that the proposed research would benefit, or at least not be harmful, to children?
- Has every effort been made to ensure that a parent is present when the research intervention is conducted? This will not only comfort the child but will enable the parent to exercise the right to end the child's participation in the research project at any time. Investigators should note that in

some cases (e.g., research into sensitive personal matters, physical examinations of adolescents, research into abuse, etc.) it may not be appropriate to have a parent present. If a parent will not be present during the course of the project, has the investigator clearly stated why in the protocol form?

- Are the personnel involved in the research, and the facility in which the research will be conducted, knowledgeable about and sensitive to the physical and psychological needs of the children and their families?
- Have the investigators taken into account the child's previous experience with illness and medical interventions? Some children may be able to cope with the stress of research better than others as a result of previous experience with medicine. Younger, "less experienced" children may be unprepared for participation in medical research.
- How has the investigator determined the number of children to be enrolled for the study? Investigators should justify the number of subjects they propose to study. Investigators should always plan to involve the fewest number of children necessary to obtain statistically significant data from which valid conclusions can be drawn.
- Whether the proposed techniques are the least invasive (physically and psychologically) in order to obtain the research information.
- Have the investigators clearly defined how the assent of the child-subjects will be obtained?
- For research involving medical interventions, the IRB will consider previous research with animals. The investigator should indicate whether the animal research is completed and the results to date.
- All research involving children as subjects must be reviewed by the full IRB unless the research is exempt from review. All personnel working with children should be familiar with the State laws requiring the reporting of suspected abuse. The IRB cannot approve research that exposes children as subjects to more than minimal risk and does not satisfy the conditions outlined above. The Federal regulations, however, provide a process for seeking approval for such research from the DHHS secretary.

Permitted Categories for Research with Children

Federal regulations classify permissible research involving children into four categories based on degree of risk and type of individual subjects. These categories are described in relation to "minimal risk":

1. **Research not involving greater than minimal risk** (45 CFR 46.404 and 21 CFR 50.51)

2. **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects** (45 CFR 46.405 and 21 CFR 50.52):

3. **Research that involves more than minimal risk and presents the prospect of no direct benefit to individual subjects, but generalizable knowledge (societal benefit)** (45 CFR 46.406 and 21 CFR 50.53):

4. **Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children** (45 CFR 46.407 and 21 CFR 50.54):

Parental Permission

By definition, children are unable to provide informed consent to participate in research, although they might be able to give their assent. The IRB should determine that unless parental permission can be waived adequate provisions are made for soliciting the permission of the parent(s) or legal guardian(s). The regulations define "permission" at 46.402(c) as the "agreement of parent(s) or guardian to the participation of their child or ward in research." The term "parent" means a "child's biological or adoptive parent." The term "guardian" means "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care."

1. Research involving **no more than minimal risk** requires permission from at least one parent (or guardian).
2. Research that involves **more than minimal risk** but presents the prospect of **direct benefit to individual subjects** requires permission from **at least one parent** (or guardian).
3. Research that involves **more than minimal risk** and presents the prospect of **no direct benefit to individual subjects**, but generalizable knowledge (societal benefit) requires permission from **both parents**.*
4. Research that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children, does **NOT provide direct benefit to the subject or societal (indirect) benefit** requires permission from **both parents**.*

NOTE: If there are two parents available to give permission but they disagree about allowing their child to participate in the study, the child should not be enrolled unless that disagreement can be resolved. This policy applies to all permissible categories of research involving children.

*Unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. If these circumstances are present, the researcher should document this in the subject's research record.

Process of Obtaining Parental Permission

Unless the IRB has granted a "Waiver of Documentation of Consent" the answer is NO. It is true that verbal permission from the parent/guardian is allowed in the clinical setting, however this is not allowed in research.

FDA Guidance contains the following information:

May informed consent be obtained by telephone from a legally authorized representative?
A verbal approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, it is acceptable to send the informed consent document to the legally authorized representative (LAR) by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it is discussed. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical investigator by facsimile.

OHRP Guidance contains the following information:

How should parental permission for research involving children be documented?

Permission by parents or guardians shall be documented in accordance with and to the extent required by 46.117 of subpart A of 45 CFR part 46. Essentially, parental permission should be documented in a manner similar to that used to document informed consent. An Institutional Review Board (IRB) may find that waiver of documentation of informed consent is appropriate under the HHS regulations at 46.117.

45CFR46.117 Documentation of informed consent.
(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

Wards of State

Children who are wards of the state or any other agency can be involved in research that is:

1. **no more than minimal risk** with permission from a guardian;
2. **more than minimal risk** but presents the prospect of **direct benefit to individual subjects** with permission from a guardian;
3. **more than minimal risk** and presents the prospect of **no direct benefit to individual subjects**, but generalizable knowledge (societal benefit) ONLY if the research is
   - related to their status as wards, or
   - conducted in schools camps, hospitals, institutions, or similar settings in which the majority of children involved are not wards.

   The IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
4. Research not otherwise approvable that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children, but does **NOT provide direct benefit to the subject or societal (indirect) benefit.** The research cannot be approved unless the criteria in #3 are met and HHS Secretary approval is granted.

NOTE: The foster parent is usually not the legal guardian of a child in foster care. Either social services or the biological parent may have legal authority for the child.

When Parental Permission is Not Needed

In Virginia, certain people under 18 years of age are legally able to consent for certain treatments or procedures. For those procedures, these minors do not fit the federal definition of "children." The IRB may determine that these individuals may consent for themselves to participate in research involving those treatments or procedures. The following information provides examples of circumstances under which Virginia law combined with federal regulations permits individuals under 18 to enroll in research without permission from parent(s) or guardian(s).

- Minors who have decision making capacity can give consent for certain treatment. Va. Code 54.1-2969(E)
  - medical or health services needed to diagnose or treat venereal disease or other infectious/contagious disease that is reported to the Virginia Dept. of Health.

  - medical or health services required in the case of birth control, pregnancy or family planning except for sexual sterilization. Consent for abortion must be obtained as required by Virginia law. Va. Code 16.1-241(V)
  - medical or health services needed for outpatient care, treatment or rehabilitation of substance abuse
  - medical or health services needed for outpatient care, treatment or rehabilitation for mental illness or emotional disturbance
- Minors who have decision making capacity and are married. Va. Code 54.1-2969(F)
- Consent for all treatment for themselves, except sexual sterilization
- Emancipated minors who have decision making capacity. Va. Code 16.1-334.
- Upon presentation of a court order documenting emancipation, can provide consent for all treatment for themselves
- Pregnant minors who have decision making capacity. Va, Code 54.1-2969(G)
- Consent for hospital admission and all treatment for herself and her child provided during the delivery of the child. Consent to subsequent surgical and medical treatment for the child.

NOTE: Virginia law may include more restrictions and exceptions than are summarized here. Researchers considering enrolling subjects whose status is uncertain should consult the relevant sections of the law.

Researchers enrolling research participants in other states or countries must comply with local law. In all cases, if the prospective subjects cannot legally consent for the treatments or procedures involved in the study, they are considered "children" by federal regulations. Conversely, if they can consent for the treatments or procedures, they are NOT "children" by federal regulations.

Child Assent

In addition to parental permission, federal regulations require that research studies involving children include adequate provisions for soliciting the assent of a child to participate in research when the child is capable of providing assent. Assent is defined as "a child's affirmative agreement to participate in research." However, the mere absence of an objection by the child should not be construed as assent.

The IRB must find that adequate provisions are made for soliciting the assent of children when, in the judgment of the IRB, the children are capable of providing assent. In determining whether children are capable of assenting, the IRB will take into account the ages, maturity, and psychological state of the children involved. When a child's assent is required, the child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity and condition.

The requirement for documenting informed consent by use of a written consent/assent form approved by the IRB and signed by the participant or the participant's legally authorized representative applies when children are the subjects of research, unless this requirement is waived by the IRB (see below). A parent (one or both) or, in some cases, a guardian must document permission for his/her child to participate in research.

If verbal consent/assent will be obtained, the IRB must review a written description of the information (i.e. consent/assent) that will be provided to the children during the assent process. As with written consent/assent, a parent (one or both) or, in some cases, a guardian must document permission for his/her child to participate in research.

The regulations do not specify an age at which assent is required. The UVA IRB-HSR requires either verbal or written documentation of assent for participation of subject's ages 7 – 17 (when determined to be appropriate) unless waived as explained below.

If an investigator chooses not to use the stand alone assent form for children ages 7-14 or the written documentation on the main consent from the minor ages 15-17, the investigators should seek verbal assent from children as appropriate to their age, maturity and psychological state. The protocol should detail the process of obtaining assent. In this case, the main consent will document the person obtaining verbal assent from the minor.

The IRB may waive assent under the following circumstances:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted;
- The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research; or
- Even where the IRB determines that the children are capable of assenting, the IRB may waive the requirement for obtaining assent under circumstances under 45CFR46.116(d) in which consent may be waived.

Difficult Issues/Sensitive Matters involving Children -

Discovery and Disclosure of Sensitive Information
In the course of research with children, especially adolescents, researchers may discover sensitive information about subjects that is not related to the study itself. For example, such information as sexual activity, STDs, use of illegal substances, and child abuse.

- ***Confidentiality***: Researchers need to consider how they will handle such situations should they arise. The permission and/or assent form should describe plans for disclosure—or non-disclosure—of such information to parents, legal authorities, and the subjects themselves. In some situations it may be appropriate to obtain a NIH *Certificate of Confidentiality*.
  - ***Child Abuse Reporting***: Additional Information

Enrolling Children in Long-Term Studies

Long-term research studies may involve subjects who are children at the time of enrollment but reach the age of consenting for themselves (in Virginia, usually 18 years old) while study procedures or follow-up are still ongoing. The IRB will consider on a protocol-by-protocol basis whether obtaining new consent from such subjects is required.

If there is continued interaction with subjects who were first enrolled as children, "re-consenting" when a subject's legal status changes will usually be required. If the only continuing study procedures are follow-up activities such as review of records or examination of biological specimens, the original consent may suffice. OHRP Guidance

PRISONERS

Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for making choices, earning money, communicating with outsiders, or obtaining medical care. The National Commission for the Protection of Human Subjects found that prisoners often volunteer for medical research as a means of access to competent medical, social service or psychological care.

Prisoner is defined to include any individual involuntarily confined or detained in a penal institution.

The term is intended to encompass individuals:

- sentenced to such an institution under a criminal or civil statute,
- individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and
- individuals detained pending arraignment, trial, or sentencing.

Persons receiving care in a medical treatment setting who are also "prisoners" as defined above, can be considered for enrollment in research **only** as permitted for other prisoners as subjects.

When a previously enrolled research subject becomes a prisoner, the Principal Investigator must notify the IRB immediately. The IRB should then promptly review the protocol in accordance with the requirements of 45CFR46 subpart C if the Principal Investigator wishes to have the prisoner subject continue to participate in the research.

Categories of Research in Which Prisoners May Participate

To protect this study population, federal regulations stipulate that the only studies that may use prisoners are the following:

- Studies of the possible causes, effects, and processes of incarceration and criminal behavior, if those studies present no more than minimal risk or inconvenience to the subjects.
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects.
- Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the secretary of the Department of Health and Human Services has consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register.
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by the secretary of the Department of Health and Human Services, after consultation with appropriate experts as described above.

The Secretary of DHHS waived the applicability of 45 CFR 46.305(a)(l) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

- In which the sole purposes are to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease, and

- Where the institution responsible for the conduct of the research certifies to the Office for Human Research Protections, DHHS, acting on behalf of the Secretary, that the IRB approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and prisoners are not a particular focus of the research.

Additional Duties of the IRB

When the IRB reviews research that will involve prisoners they are required to first confirm that the proposed study fits within the permissible categories of research described above. Then, it must determine:

- Any advantages that prisoners will realize as a result of participation in the research, when compared to general living conditions within the prison, are not so great as to impair the prisoner's ability to weigh the risks and benefits of participation and freely choose.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (usually demonstrated by enrolling non-prisoner subjects from the community, as well).
- Procedures for selecting subjects within the prison are fair, and free from arbitrary manipulation by prison authorities or other prisoners.
- Control subjects will be selected randomly from among the group of eligible volunteers, unless the principal investigator justifies a different procedure.
- The information presented during recruitment and consent procedures is in a language, and level of complexity, understandable to the subject population.
- The IRB is assured that the parole board will not take research participation into account in making decisions about parole, and each prisoner is informed in advance that participation will have no effect on the possibility of parole.
- If medical follow-up is necessary to protect the health and welfare of the subjects, adequate provision is made for such care, taking into account the varying length of prisoners' sentences.

Finally, an IRB that reviews research involving prisoners is required to have at least one member who is either a prisoner, or a prisoner representative; and a majority of the IRB members cannot be in any way associated with the prison(s) involved. (This requirement may be waived if two or more IRBs are involved in reviewing the same protocol, and at least one of the IRBs meets this condition.)

STUDENTS AND EMPLOYEES

Investigators should detail any extra precautions taken to safeguard the rights and welfare of subject populations. In the case of using employees or a student "subject pool," the IRB should ensure that consent for participation is sought only under circumstances, which minimize the possibility of coercion or undue influence, and that genuinely equivalent alternatives to participation are available.

Students

It is not uncommon for research projects to involve students, either those enrolled in a specific course or those enrolled in university programs. For instance, it is common practice for medical students to serve as subjects in biomedical research or for psychology students to serve as subjects in behavioral research. The obvious concern is that their participation may not be truly voluntary, because of a desire to appear particularly cooperative or highly motivated, or because participation in research is a course requirement.

Various procedures have been suggested to reduce the possible unintended coercion, while still permitting students to participate as subjects in research. These include:

- Posting IRB approved advertisements throughout the university to recruit subjects from a broad base of students.
- Offering students the opportunity to participate in "mass screenings" with follow-up with those who meet research criteria. It should be clearly stated that participation in the screening, as well as participation in the research is voluntary.
- Avoiding any personal solicitations by students, faculty, GTAs or RAs for fellow students or faculty.
- Providing a number of research projects from which to chose, if participating as a research subject is a course requirement.
- Providing alternative and equal methods for meeting course credit (or extra credit) requirements, such as attending a series of research presentations by faculty, writing a brief paper, conducting one's own research.

Researchers need to exercise special caution when they desire students in a class to participate in research at the same time. Unintended coercion must be avoided by (1) ensuring that participation is voluntary, (2) that no one knows who is and is not participating, and (3) a time and effort equivalent alternative is provided for those who wish not to participate. Course grades should not be based on research participation. Basing grades on research participation is coercive and should be avoided.

A researcher should not have access to the data collected until after the class grades have been posted. Researchers often ask a colleague not affiliated with the research or class to administer the evaluation and hold the data until after the grades are posted.

Employees

University employees, such as faculty, office staff, lab technicians, and postdoctoral fellows, are similar to students in that they are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor's work. Accordingly, many of the same procedures described above to reduce the likelihood of coercion in recruiting student volunteers apply equally to university employees.

COGNITIVELY IMPAIRED PERSONS

All adults (including those with cognitive impairments) are presumed competent to consent unless legally judged to be incompetent.

Cognitively impaired persons are considered a vulnerable research population because their mental disability may compromise their capacity to make a reasoned decision about participation in a study.

People with Alzheimer's disease, dementia, mental illness and developmental disabilities may be considered cognitively impaired and may not be able to provide informed consent for participation in research.

In certain circumstances, when it is determined that a potential research participant is cognitively impaired, federal regulations and state statute permit researchers to obtain consent from a legally-authorized representative via Surrogate Consent).

For research protocols involving subjects who have fluctuating or limited decision-making capacity or prospective incapacity, Principal Investigators should establish and maintain ongoing communication with involved caregivers, consistent with the subjects' autonomy and with medical confidentiality.

The National Bioethics Advisory Commission issued a report on *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity* (December 1998). The recommendations set forth in that report should be carefully reviewed by Principal Investigators considering research involving such a population. Some of the requirements or considerations discussed in the report include:

Determining Decision-Making Capacity

A primary consideration when recruiting subjects with severe cognitive or psychiatric disorders is to establish procedures for determining which individuals are able to provide legally valid consent, and which are not.

The protocol reviewed by the IRB must detail a specific plan for the assessment of the decision-making capacity of the subject. The assessment will be conducted by the investigator for any subject who may qualify for Surrogate Consent . While there are no standardized measures for determining capacity to consent, subjects may be assessed on their ability to understand and to express a reasoned choice concerning the:

- Nature of the research and the information relevant to his/her participation;
- Consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- Consequences of the alternatives to participation.

The capacity to understand all of these concepts may not be necessary in order to consent to participate in a particular research protocol -- greater capacity is required for higher-risk protocols. This assessment should be used for determining the capacity of the surrogate as well, if necessary.

In protocols in which Surrogate Consent has been approved by the IRB, assessment of the decision-making capacity of the surrogate should be implemented only when the investigator has reason to believe that the subject's decision-making capacity may be impaired.

Consent for Cognitively Impaired

To have the option to obtain assent from a subject's legally-authorized representative, the investigator must request the use of Surrogate Consent .

When assent will be obtained from a legally-authorized representative (surrogate), the IRB usually will require that the assent of the subject be obtained.

Assent is defined as affirmative agreement to participate in research. Failure to object does not qualify as assent.

For information, see Assessing Decision-Making Capacity and use of Surrogate Consent .

Surrogate Consent

Surrogate Consent for participation in a research study should be employed only to the extent that it is consistent with the intent of 45 CFR 46.116, 45 CFR 46 and 21 CFR 50.20 and all other federal and state laws and regulations pertaining to protecting human subjects participating in research

This would be necessary when an adult is not able to provide consent for themselves to participate in research due to:

- cognitive impairment,
- lacking capacity, or
- suffering from a serious or life-threatening disease

While no specific set of criteria can encompass all conceivable situations in which the use of Surrogate Consent complies with the intent of 45 CFR 46.116 and 21 CFR 50.20, the following criteria should be viewed as fundamental guidelines to be used by the UVa IRBs when determining whether to permit the use of Surrogate Consent for participation in a research study.

- Surrogate Consent is a protocol-specific request of the investigator, and must be reviewed and approved accordingly by the IRB.
- Surrogate Consent is requested through the protocol for new research studies or through the modification process for an existing protocol.
- As in all human subject's research, the IRB must consider carefully the risk/benefit ratio of the particular study for the targeted population.
- As with all mental health research conducted by the University, subject confidentiality and privacy must be protected.
- The IRB may consider whether the frequency of a specific protocol's review cycle should be reasonably modified when Surrogate Consent is implemented.

In order to allow Surrogate Consent the following criteria must be met:

- As in all protocols, the IRB must carefully review the risks and benefits for the participants.
- Surrogate Consent will only be appropriate when it is clear that individuals cannot give informed consent.
- Where appropriate, animal and other pre-clinical studies must have been conducted which suggest that there is reason to believe that the proposed investigation may have potential for therapeutic benefit to the participant and/or that the study meets exempt or expedited approval criteria. The requirement for potential therapeutic benefit need not apply to any control group.
- A line must be added to the consent form for the signature of the person giving Surrogate Consent along with a line explaining the relationship to the participant.
- The investigator shall include a specific plan for the assessment of the decision-making capacity of the subject in the protocol or modification request. If the investigator determines that the subject lacks decision-making capacity, the investigator shall, consistent with the standard consent process describe the research to the subject and the investigator's intent to obtain Surrogate Consent; and document this communication in the research file confirming that the research protocol was described to the subject. However, if the investigator determines that the subject is non-responsive, the investigator shall document that observation in the research file.
- If the subject expresses resistance or dissent to participation or to the use of Surrogate Consent by word or gesture, the subject shall be excluded from the research study.

Guidance to Investigators Concerning Who May Act as a Surrogate or Legally Authorized Representatives (LAR)

In studies where Surrogate Consent is approved, the consent should be obtained from a decision maker using the hierarchy below. Surrogate consent should be obtained from the person highest on the list who is available, willing and capable.

1. The agent previously appointed by the prospective subject when competent, in an advance directive that specifically authorized decisions about participation in research;
2. Legal guardian of the prospective subject;
3. Spouse of the prospective subject, except where a suit for divorce has been filed and the divorce decree is not yet final;
4. Adult child of the prospective subject;
5. Parent of the prospective subject when the subject is an adult;
6. Adult brother or sister of the prospective subject;

Potential LARs in emergency circumstances must be advised that if a higher-ranking LAR is identified and able to be consulted at a later time, the investigator will defer to the higher-ranking LAR's decision regarding the subject's participation in the research.

If a higher ranking LAR is identified after consent has been obtained, the higher ranking LAR must be contacted and informed of the study. He/she should be given a copy of the signed consent form and any communications with him/her should be documented in a note to file. A decision by a higher-ranking LAR to withdraw the subject from the research should be handled the same way one would handle a decision by the subject to withdraw if he/she becomes able to give consent for themselves. LARs and subjects considering withdrawal from a study should be fully informed about any clinical risks of withdrawing, such as feasibility, risks of removing inserted devices.

PREGNANT WOMEN, FETUSES, AND NEONATES

Research involving pregnant women, fetuses and human in vitro fertilization are subject to special federal regulations that guide IRB deliberations on such studies.

Research studies involving **pregnant women or fetuses** can be approved by the IRB if the following requirements of federal regulations are satisfied:

- Preclinical studies have been conducted, including studies on pregnant animals; clinical studies, that include nonpregnant women and provide data for assessing potential risks to pregnant women and fetuses
- Risk to fetus is caused solely by interventions or procedures that hold prospect of direct benefit for the woman or the fetus or,
- If no benefit, risk to the fetus is not greater than minimal and the research develops important biomedical knowledge not obtainable by any other means.
- Any risk is the least possible for achieving the objectives of the research.
- Individuals engaged in the research will have no part in: 1) any decisions as to the timing, method, or procedures used to terminate a pregnancy, and 2) determining the viability of the fetus at the termination of the pregnancy; and
- No inducements, monetary or otherwise, will be offered to terminate the pregnancy.

Definitions:

Fetus means the product of conception from implantation until delivery.

Neonate means a newborn.

Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements for research involving children.

Active Recruitment of Women

In order to assure that adequate numbers of women are included, researchers are encouraged to actively recruit women into clinical drug trials. For specific outreach methodologies, researchers should refer to the NIH Outreach Notebook of the Inclusion of Women and Minorities in Biomedical and behavioral Research (1994).

Women of Child-Bearing Potential

Historically, in order to avert harm to a developing fetus in an unsuspected pregnancy, physicians and the lay community expressed concerns regarding the participation of women of child-bearing potential in research. As a result, Federal agencies developed special guidelines for the protection of the developing fetus that excluded women of child-bearing potential from participation in some research. In 1977, for example, the FDA published a guideline that excluded most women of child-bearing potential from early phase drug trials. An exception was made for studies involving women with serious and life-threatening diseases.

Since then, questions raised by grass roots, professional consumer, and governmental groups regarding the adequacy and fairness in the distribution of the risks and benefits of research resulted in changes to the regulations for the involvement of women in research. At the same time, improved pregnancy tests and methods of contraception became available.

FDA Guidance

In 1988, the FDA issued guidelines that called for safety and efficacy profiles for women, elderly, and diverse racial groups as part of new drug applications (NDA). Then in 1993, following a broad public discussion about participation of women in clinical drug trials, the FDA issued a new guideline that eliminated restrictions on women of childbearing potential in all phases of drug trials.

The guideline detailed procedures for minimizing the risks of pregnancy in women participants, such as contraceptive counseling, pregnancy tests, timing of short term studies in relation to the menstrual cycle, and the process of informed consent. Though the FDA emphasized the importance of risk/benefit determinations for subjects entering various phases of clinical drug trials, they underscored that initial determinations regarding whether risks to a fetus were adequately addressed were best left to subjects, physicians, local IRB's, and study sponsors. The new guideline also called for gender analysis with special attention to factors affecting the role of the menstrual cycle, and exogenous hormone therapy in relation to the drug, as well as the influence of the drug on oral contraceptives.

DHHS Guidance

The Department of Health and Human Services has also carefully examined the issue of participation of women of child bearing potential in research. Since the primary aim of clinical trials is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine if the intervention or therapy being studied affects men and women differently. As stated in its guidelines, NIH Outreach Notebook of the Inclusion of Women and Minorities in Biomedical and Behavioral Research (1994), the NIH has concluded that the inclusion of women in research is sufficiently important that the only justifiable reason to exclude non-pregnant women of child-bearing potential from research is compelling evidence that the proposed research would be inappropriate with respect to the health of the subject or to the purpose of the research.

The policy statement referenced above pertains primarily to the inclusion of women as subjects in clinical trials, i.e., medical research testing new treatments. However, the inclusion of women in behavioral research is also important and should be accomplished unless there is a compelling rationale which establishes that inclusion is inappropriate with respect to the health of the subject or the purpose of the research.

Significant portions of the text below are presented verbatim as published in the Code of Federal regulations and the Federal Register.

Pregnant Women as Human Research Subjects

Drug research using pregnant women as subjects is governed by the federal regulations. In accordance Federal Regulations, "no pregnant woman may be involved as a subject in a human clinical research project unless:

(1) the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or
(2) the risk to the fetus is minimal. "

Research involving pregnant women is permitted only if the mother and the father are legally competent and both have given their consent after having been fully informed regarding the possible impact on the fetus, except that the father's consent need not be secured if

(1) the purpose of the activity is to meet the health needs of the mother;
(2) his identity or whereabouts cannot be reasonably ascertained;
(3) he is not reasonably available; or
(4) the pregnancy resulted from rape.

Women of Child-Bearing Potential as Human Research Subjects

Non-pregnant women should not be excluded from any phase of research unless the science of the project or the health of the subject will be compromised. Regarding clinical drug research, Phase I, II and III trials should have the proportion of women in the study which at least reflects the proportion of women in the population that will receive the drug when it is marketed, and should enroll numbers adequate to detect clinically significant sex differences in drug metabolism and response.

Risk to Fertility

It is expected that both male and female subjects will be informed about potential risks to their fertility including the development of any abnormalities or abnormalities in function of reproductive organs as a consequence of the proposed study intervention. "Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals as a consequence of the proposed study intervention, the decision to include subjects of reproductive age in a clinical study should be based on a careful risk/benefit evaluation, taking into account the nature of the abnormalities, the

dosage needed to induce them, the consistency of the findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment, and the duration of therapy.

"Where subjects of reproductive potential are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate monitoring and/or laboratory studies to allow detection of these effects. Long-term follow-up will usually be needed to evaluate the effects of such drugs in humans.

Risk to Fetus and/or Infant

- **General Guidelines:** "Appropriate precautions should be taken in research studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and subjects of potential risk and the need for precautions. In all cases, the informed consent document and investigator's drug information brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. If these studies have not been completed, other pertinent information should be provided, such as general assessment of fetal toxicity in drugs with related structures or pharmacological effects. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk. "In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of child-bearing potential, i.e., usually by the end of Phase II and before any expanded access program is implemented.
- **Minimizing the Possibility of Fetal Exposure:** "Pregnancy testing may be used to detect unsuspected pregnancy prior to initiation of study treatment. Timing of the start of the study to coincide with or immediately following the onset of menses is also an adequate indication that the subject is not pregnant. The investigator should ascertain that the subjects will responsibly employ a reliable method of contraception or abstinence for the duration of the drug or treatment exposure, which may exceed the length of the study. If requested, the investigator should be able to refer the subject to a knowledgeable counselor or physician for contraception advice."
- **Inclusion of Women in Early Clinical Trials (Phase I and Early Phase II):** "In some cases, there may be a basis for requiring [inclusion] of women in early studies. When the disease under study is serious and affects women, and especially when a promising drug for the disease is being developed and made available rapidly under FDA's accelerated approval or real access procedures, a case can be made for requiring that women [be allowed to] participate in clinical studies at an early stage. When such a drug becomes available under expanded access mechanisms (for example, treatment INDS or parallel track) or is marketed rapidly under subpart E procedures because an effect of survival or irreversible morbidity has been shown in the earliest controlled trials, it is medically important that a representative sample of the entire population likely to receive the drug has been studied, including representatives of both genders. Under these circumstances, clinical protocols should not place unwarranted restrictions of participation of women.
- **Risk to Infant of Nursing Mother:** The potential for harm from exposure to a drug with unknown risks exists for nursing infants, as well as fetuses. Therefore, this policy applies to breast feeding female subjects who are potential subjects in a drug trial in the same manner in which it applies to gestating women.

Research Involving Human *In Vitro* Fertilization

The Federal regulations require that all investigators proposing research involving human in vitro fertilization with or without embryo transfer must submit a protocol to the IRB for review. In order to obtain Federal funding for the research, the project must receive review by a national Ethics Advisory Board. The IRB may consult with the American College of Obstetricians and Gynecologists (ACOG) and/or the American Fertility Society (AFS) when reviewing protocols involving human in vitro fertilization.

The greatest problem regarding in vitro fertilization for the IRB involves the use of "spare" embryos. Consent forms for all in vitro fertilization procedures should address what will happen to embryos that are not used in the particular embryo transfer procedure for which they were created (e.g., will they be used for research purposes, will they be implanted in other women, will they be destroyed, etc.)

Research Directed Toward the Fetus *In Utero*

Three circumstances may affect in utero research. In the first, the study is directed toward pregnant women, in which the fetus is indirectly involved in the research. In the second, the study is directed toward the fetus, that is, the fetus is the research subject. Finally, there are situations where both the pregnant woman and the fetus are the subjects of the research.

The IRB may only approve in utero research when one of the following two criteria are met in addition to all other applicable institutional, Federal, State and local requirements.

- The purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (for example a new technique for fetal transfusion for Rh incompatibility); or
- The research poses no more than minimal risk to the fetus and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

Research Involving the Fetus *Ex Utero*

The Federal regulations indicate that an ex utero (delivered) fetus is viable if, in the judgment of the physician, it is likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. If the expelled or delivered fetus is viable, the regulations for research involving children will apply.

A **non-viable fetus** is defined by the Federal regulation as "an expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered fetus is non-viable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance." Research involving a non-viable fetus that would either artificially maintain vital functions or hasten their failure is forbidden by Federal regulations. Ethical considerations require respect for the dignity of the dying human subject and an avoidance of unseemly intrusions into the process of dying for research purposes.

Research with Dead Fetuses, Fetal Material, and the Placenta

Investigators are required to conduct research involving human fetuses, fetal material, and the placenta according to the following regulatory requirements:

Separating Abortion from Research

1. The decision to terminate a pregnancy and procedures of abortion must be kept independent from the retrieval and use of fetal tissue.

2. The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

Prohibiting Payments and Other Inducements

Payments and other forms of remuneration with the procurement of fetal tissue are prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissue.

Informed Consent

- Potential recipients of fetal tissue, as well as research and health care participants should be informed about the source of the tissues in question. This information should be provided to prospective subjects in the informed consent form.
- The decision and consent to terminate pregnancy must precede discussion of the possible use of the fetal tissue in research and any request for such consent that might be required for that use.
- Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. Her consent to donate fetal remains is sufficient for the use of fetal tissue.
- Consent should be obtained in compliance with Federal and State law.

Prohibiting Direct Donations

- The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue.
- Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team.
- Experimental transplants performed with fetal tissue from induced abortions by a family member, friend, or acquaintance should be prohibited.

Compliance with State and Local Laws

Research utilizing fetal tissue should comply with all applicable state laws and local ordinances. Currently, Virginia statutes are silent concerning research utilizing fetal tissue. Investigators are reminded that state law periodically changes, and does vary from state to state. Investigators conducting research outside of Virginia should be familiar with the applicable requirements of the state or country where the research is to take place.

Researchers considering conducting stem cell research in Virginia using embryos should consult current Virginia law. The Virginia human cloning statute, Va. Code 32.1-162.21-22, currently forbids "the possession of the product of human cloning" and defines "human cloning" as the creation of or attempt to create a human being by transferring the nucleus from a human cell from whatever source into an oocyte from which the nucleus has been removed. Also, as noted above, the applicable law varies from state to state, and so investigators conducting research outside of Virginia should be familiar with the requirements of the state or country where the research is to take place.

Research in Anticipation of Abortion

After lengthy review, the National Commission determined that there is no difference between the moral status of a fetus destined for abortion and that of a fetus which is expected to be carried to term. Therefore, only those research procedures that are acceptable for a fetus going to term may be performed

in anticipation of abortion, to preserve the mother's right to change her mind about ending the pregnancy.

Consent Signature Requirements

The **mother's consent** is required when the research holds:

- the **prospect of direct benefit to the pregnant woman**, or
- the prospect of a **direct benefit** both to the **pregnant woman and the fetus**, or
- **no prospect of benefit for the woman nor the fetus** but **risk to the fetus is not greater than minimal** and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;

Consent from the mother *and* father is required (unless the father is absent, incompetent, unknown or the pregnancy resulted from rape/incest) when the research holds out the prospect of **direct benefit solely to the fetus**.

Consent Decision Chart for Pregnant Women and Fetuses

	Direct benefit to mother only	Direct benefit to mother and fetus	Direct benefit to fetus only	No direct benefit or societal benefits only
Risk is more than minimal	Mother's consent	Mother's consent	Mother and father's consent	*NOT APPROVABLE BY IRB*
Risk is no more than minimal	Mother's consent	Mother's consent	Mother and father's consent	Mother's consent

MINORITIES

In addition to requiring the equitable selection of women as research subjects, Federal regulations require the equitable selection of minorities as research subjects. The inclusion of minorities in research is important both to ensure that they receive an equal share of the benefits of the research and to ensure that they do not bear a disproportionate burden.

Most research will affect all population groups. In order to contribute to the pool of generalizable knowledge, investigators are required to include the widest possible range of population groups in the research. However, sometimes minorities are subject to a different risk. For example, some research pertains to conditions such a sickle cell anemia or Tay Sachs disease that specifically affect only a few minority groups. Other research focuses on characteristics of diseases or effectiveness of therapies in particular populations (e.g., HIV transmission, treatment for hypertension), and may concern conditions or disorders that disproportionately affect a certain racial or ethnic group. Exclusion or inappropriate representation of these groups, by design or inadvertence, would be unjust. Further, to the extent that participation in research offers direct benefits to the subjects (in HIV research, for example, the receipt of a promising new drug), under-representation of minorities

denies them, in a systematic fashion, the opportunity for direct benefit. A glaring example of this type of research abuse of minority population's bearing the burden of research can be found in the United States Public Health Service Tuskegee Study of Untreated Syphilis in the Negro Male (Tuskegee Syphilis study), in which a group of African-American men suffering from syphilis were left untreated, despite the availability of penicillin, in order to study the natural course of the disease. Due to these concerns, the Federal regulations require that research design include diverse populations.

ECONOMIC OR EDUCATIONALLY DISADVANTAGED

The Department of Health and Human Services recognizes that certain populations may require additional protections because they are economically or educationally disadvantaged. The IRB will attempt to safeguard every subject's rights and welfare by making sure that any possible coercion or undue influence is eliminated (e.g., compensation that is not commensurate with risk, discomfort, or inconvenience involved, or recruiting in institutional settings where voluntary participation might be compromised).

TERMINALLY ILL SUBJECTS

Subjects with a terminal illness may be willing to "try anything" that might offer hope of either a cure or a slowing of the disease process. Others, aware that nothing further can be done to cure their disease, might fear abandonment by the medical establishment and agree to participate in research as a means of maintaining contact with physicians expert in treating their condition. On the other hand, many terminally ill individuals are willing to submit to considerable discomfort and risk for the possible benefit of future subjects suffering from the same condition, and will volunteer for Phase I clinical trials or basic research about their particular condition in hopes of helping other, similarly situated subjects in the future.

Investigators should be sensitive to these matters and explain with care and clarity the likelihood (or lack thereof) that research subjects will experience any personal medical benefit from their participation in a particular study. This is especially important in Phase I drug studies, since the research is designed to evaluate a potential treatment for their illness and as a result, may obscure the fact that the dosage subjects will be given is not expected to produce a therapeutic result. At the same time, it is important not to treat terminally ill subjects as incompetent or incapable of autonomous decision-making, just because they are critically ill.

AIDS/ HIV+ Subjects

Subjects involved in HIV-related research (HIV-infected persons and persons at risk of HIV-infection) are particularly vulnerable because of their disease status and because the disease disproportionately affects certain populations.
Principal Investigators should be aware of the numerous ethical concerns presented by HIV, including considerations of confidentiality, privacy and justice and follow Virginia State regulations.
An overriding concern in HIV research is confidentiality and privacy, since breaches of confidentiality could have severe adverse consequences.
In ensuring that research adequately protects subjects' confidentiality, Principal Investigators should consider the following criteria:

- where identifiers are not required by the study design, they are not to be recorded.
- if identifiers are recorded, they should be separated, to the greatest extent possible, from data and securely stored, with linkage restored only if necessary to conduct the research.

- if subjects will be given a fair and clear explanation of how information about them will be handled, including whether and how the information will be recorded in their medical records.
- whether the protocol will specifically set forth how to respond to attempts to force disclosure of subjects' medical records or requests by third parties who have authorizations for disclosure signed by subjects; and
- whether the protocol will clearly state what information will be recorded, who is entitled to see records with identifiers, and whether any state laws require the reporting of HIV infection or the disclosure of other information.

Sharing of HIV Test Results

In research protocols that involve HIV testing, investigators should consider the circumstances under which subjects should or must be told of their HIV sero status. In general, IRB policy requires that individuals whose test results are associated with personal identifiers be informed of their HIV test results and provided the opportunity to receive counseling, unless the situation is a special circumstance calling for an exception (*e.g.* , compelling evidence that a given individual would attempt suicide if informed that he/she is seropositive). When individuals will be informed of their HIV antibody test results, Principal Investigators should ensure that the protocol provides for appropriate pre-test and post-test counseling.

BASIC ELEMENTS OF THE PROTOCOL

The following outlines the basic elements of a research protocol. The IRB templates will provide more specific requirements.

Table of Contents

Sponsor's protocols typically include a table of contents. The UVA IRB protocol templates do not require a table of contents.

Introduction/ Abstract

The introduction should indicate the specific reasons or rationale for performing the study, the hypotheses, study design (*e.g.*, record review, questionnaire, specimen collection, interview, prospective evaluation of a drug or device), and an overview of the literature on comparable studies. If applicable, Principal Investigators should briefly describe the intervention, treatment, drugs, or devices to be used.

Hypothesis

A hypothesis is a tentative statement that proposes a possible explanation to some phenomenon or event. A useful hypothesis is a testable statement which may include a prediction. The key word is testable. That is, the researcher will perform a test of how two variables might be related. This is when the researcher is doing a real experiment. The researcher is testing variables.

Objectives and Rationale

The objectives of the study should be:

- based on the research question(s);

- limited in scope and number;
- based on specific quantifiable endpoints; and
- congruent with the study design.

The scientific rationale should provide enough information to answer the question, "Why should this study be done?" It should contain a referenced review of the literature specifically pertaining to the reasons for the current study and previous investigations that lead the investigator to pose the specific question. In addition, it should include a justification of the research design and the use of any placebos.

Methods and Procedures

This section describes the study design, the study population, the research intervention, if applicable, sample selection, and an appropriate analytic plan. Specific recommendations for presenting study methods are presented below.

For Clinical Research

The Methods section for clinical study protocols evaluating a drug, device or a treatment modality should explain the treatment plan. Baseline diagnostic tests, initial laboratory assessments for determining eligibility of a potential subject to enter the trial, and any procedures, physical exams, tests, interviews, videotapes, and the amount of time the subject will be involved in the study should be detailed. Principal Investigators should consider including a table or schematic of study events by visit to clarify for the IRB reviewers what tests, procedures, etc. will be done and when they will be done.

Principal Investigators should make clear which interventions and procedures are standard clinical care for the subject's condition and which are experimental or, if not experimental, are being performed solely as a result of the subject's participation in the clinical research.

Principal Investigators should discuss (1) the procedures for monitoring the subject's condition and (2) reasons for dropping any participant from the study *(e.g.*, relapse, lack of subject compliance).

Subject Population Selection and Inclusion/Exclusion Criteria

Subject Selection and Inclusion Criteria

UVA recognizes its responsibility to create an environment in which the equitable selection of research participants is fostered. Therefore, Principal Investigators must provide the IRB the details on the proposed involvement of humans in the research. Principal Investigators must describe the number of subjects and observations necessary to obtain statistically valid results. The type of study design and the procedures for randomization, blinding, crossover, controls (positive and negative), and, washout, as applicable, must all be explained. Principal Investigators must specify the

- characteristics of the subject population,
- numbers of subjects (*i.e.*, the number of subjects required to obtain statistically valid results),
- age ranges of subjects,
- health statuses of subjects, and
- the gender composition and racial/ethnic composition of the subject population. If ethnic, racial and gender estimates are not specified, the Principal Investigator must provide a clear rationale for exclusion of this information.

Methods for subject screening and eligibility should be described in detail. Screening for enrollment into a study entails careful evaluation of the potential subject on the basis of the criteria that are stated in the protocol.

Subject eligibility criteria should be listed, including age, sex, race/ethnicity, and other inclusion and exclusion criteria. If a potential subject conforms to those preliminary criteria, more specific screening evaluations can be performed, such as the taking of a medical history, a physical examination, and clinical laboratory tests, such as a complete blood count with differential; blood chemistry analysis (*e.g.*, electrolytes, cholesterol, and triglycerides), urinalysis, an electrocardiogram, and blood pressure.

The protocol should state the limits of acceptability for the aforementioned evaluations; for example, it should define a normal range for the clinical laboratory tests and include appropriate statements about the interpretation of those tests (*e.g.* statements on borderline values).
If the proposed study may include a vulnerable or special subject population, investigators shall refer to the additional requirements for these subject populations.

Subject Exclusion Criteria

Exclusion criteria may include pregnant women (unless the research is on pregnancy), severity of disease, mental incompetence, use of other medication concomitantly, or presence of other diseases. Principal Investigators must explain and justify the exclusion of women and/or minority groups and children

Women and Minorities

All research involving human subjects should be designed and conducted to include members of both genders and members of minority groups, unless a clear and compelling rationale and justification establishes that such inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

The NIH acknowledges clear scientific and public health reasons for specifically including members of minority groups in studies of health problems that disproportionately affect U.S. racial/ethnic minority populations. In attempting to include minority groups, Principal Investigators should assess the theoretical and/or scientific connections between race/ethnicity in the topic of study. FDA Guidelines require that subjects recruited to trials reflect the population that will receive the drug/therapeutic intervention when it is marketed or approved for administration. FDA Guidelines also recommend that "representatives of both genders be included in clinical trials in numbers adequate to allow detection of clinically significant gender related differences in drug response."

For NIH-defined Phase I and II clinical trials, the systematic inclusion and reporting of information on women and minorities and minority subpopulations is generally required to increase the scientific base of knowledge about them. For Phase III clinical trials, the design of the trials must reflect the current state of knowledge about any clinically important gender and/or race/ethnicity differences in the response to the intervention. Evidence may include data from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, epidemiologic and other relevant studies. The nature of the evidence should be used to determine the extent to which women, men and members of minority groups and their subpopulations must be included. In addition, national statistics on the disease, disorder or condition under study and national population statistics should be used in designing Phase III clinical trials.

Studies should employ a design with gender, racial and/or age representations appropriate to the known incidence/prevalence of the disease or condition being studied. If subjects of a certain gender, race or age group are to be excluded and it can reasonably be assumed that the drug or therapeutic intervention when approved will be administered to both sexes and all age and racial groups, the investigator **must** clearly explain and justify such exclusion.

It is not expected that every minority group and subpopulation will be included in each study; however, broad representation and diversity are the goals, even if multiple clinics and sites are needed to accomplish it.

Minority groups recognized by NIH include:

- American Indian or Alaskan Native (person having origins in any of the original peoples of North America, and who maintain cultural identification through tribal affiliation or community recognition);
- (ii) Asian or Pacific Islander (person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent or the Pacific Islands and Samoa);
- (iii) Black, not of Hispanic origin (a person having origins in any of the black racial groups of Africa); and
- (iv) Hispanic (a person or Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin regardless of race).

Each minority group may contain subpopulations which are delimited by geographic origins, national origins and/or cultural differences. The minority group or subpopulation to which an individual belongs is determined by self-reporting.

Subject Withdrawal Criteria

A protocol shall include subject withdrawal criteria and procedures specifying

- when and how to withdraw subjects from the trial,
- the type and timing of data to be collected for withdrawn subjects,
- whether and how subjects will be replaced, and
- the follow-up for such subjects.

If data collected for research purposes has clinical significance for individuals in the study but the data will be analyzed at another institution, resulting in substantial delay in receipt of important clinical findings affecting the subject's welfare, Principal Investigators should specify how they intend to monitor the subject locally.

Risks and Benefits

Background

Per DHHS and FDA regulations (45 CFR 46.111 and 21 CFR 56.111) two of the required criteria for granting IRB approval of the research are:

- Risks to subjects are *minimized* by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are *reasonable* in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.

Definitions

- **Benefit:** A valued or desired outcome; an advantage.

- **Risk:** The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."
- **Minimal Risk:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily lives of the general population or during the performance of routine physical or psychological examinations or tests.
- **Minimal Risk for Research involving Prisoners:** The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. Minimal risk is in this case is defined as, "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examinations of healthy persons."

Overview of Risks and Benefits

There are two sources of confusion in the assessment of risks and benefits. One arises from the language employed in the discussion:

- "Risk" is a word expressing probabilities;
- "Benefits" is a word expressing a fact or state of affairs.

It is more accurate to speak as if both were in the realm of probability: i.e., risks and expected or anticipated benefits.

Confusion also may arise because "risks" can refer to two quite different things:

- those chances that specific individuals are willing to undertake for some desired goal; or
- the conditions that make a situation harmful to a subject.

Researchers should provide detailed information in the IRB protocol about potential risks and benefits associated with the research, and provide information about the probability, magnitude and potential harms associated with each risk.

Risk/Benefit Assessment

The IRB is responsible for evaluating the potential risks and weighing the probability of the risk occurring and the magnitude of harm that may result. It must then judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies inviting any person to undertake the risks. The IRB cannot approve research in which the risks are judged unreasonable in relation to the anticipated benefits. The IRB must:

- Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
- Determine that the risks will be minimized to the extent possible [see below];
- Identify the probable benefits to be derived from the research;
- Determine that the risks are reasonable in relation to be benefits to subjects, if any, and the importance of the knowledge to be gained; and

- Assure that potential subjects will be provided with an accurate and fair description (during consent) of the risks or discomforts and the anticipated benefits.

Types of Risk to Research Subjects

The risks to which research subjects may be exposed have been classified as physical, psychological, social, and economic.

Physical Harms: Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. All of these should be considered "risks" for purposes of IRB review. Some of the adverse effects that result from medical procedures or drugs can be permanent, but most are transient.

Some medical research is designed only to measure more carefully the effects of therapeutic or diagnostic procedures applied in the course of caring for an illness. Such research may not entail any significant risks beyond those presented by medically indicated interventions. On the other hand, research designed to evaluate new drugs or procedures may present more than minimal risk, and, on occasion, can cause serious or disabling injuries.

Psychological Harms: Participation in research may result in undesired changes in thought processes and emotion (e.g., episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem). These changes may be transitory, recurrent, or permanent. Most psychological risks are minimal or transitory, but some research has the potential for causing serious psychological harm.

Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics such as drug use, sexual preferences, selfishness, and violence. These feelings may be aroused when the subject is being interviewed or filling out a questionnaire. Stress may also be induced when the researchers manipulate the subjects' environment - as when "emergencies" or fake "assaults" are staged to observe how passersby respond. More frequently, however, is the possibility of psychological harm when behavioral research involves an element of deception.

Invasion of privacy is a risk of a somewhat different character. In the research context, it usually involves either covert observation or "participant" observation of behavior that the subjects consider private.

The IRB must make two determinations:

- is the invasion of privacy involved acceptable in light of the subjects' reasonable expectations of privacy in the situation under study; and
- is the research question of sufficient importance to justify the intrusion?

The IRB must also consider whether the research design could be modified so that the study can be conducted without invading the privacy of the subjects.

Breach of confidentiality is sometimes confused with invasion of privacy, but it is really a different risk. Invasion of privacy concerns access to a person's body or behavior without consent; confidentiality of data concerns safeguarding information that has been given voluntarily by one person to another.

Some research requires the use of a subject's hospital, school, or employment records. Access to such records for legitimate research purposes is generally acceptable, as long as the researcher protects the confidentiality of that information. However, it is important to recognize that a breach of confidentiality may result in

psychological harm to individuals (in the form of embarrassment, guilt, stress, and so forth) or in social harm (see below).

Social and Economic Harms: Some invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity are information regarding alcohol or drug abuse, mental illness, illegal activities, and sexual behavior. Some social and behavioral research may yield information about individuals that could "label" or "stigmatize" the subjects. (e.g., as actual or potential delinquents or schizophrenics). Confidentiality safeguards must be strong in these instances.

Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective subjects during the consent process.

Ways to Minimize Risk

- Provide complete information in the protocol regarding the experimental design and the scientific rationale underlying the proposed research, including the results of previous animal and human studies.
- Assemble a research team with sufficient expertise and experience to conduct the research.
- Ensure that the projected sample size is sufficient to yield useful results.
- Collect data from standard-of-care procedures to avoid unnecessary risk, particularly for invasive or risky procedures (e.g., spinal taps, cardiac catheterization).
- Incorporate adequate safeguards into the research design such as an appropriate data safety monitoring plan, the presence of trained personnel who can respond to emergencies, and procedures to protect the confidentiality of the data (e.g., encryption, codes, and passwords).

Provisions for Treatment of Adverse Events

Principal Investigators should conduct a detailed and appropriate literature review, and should detail:

- all possible risks to the subject, whether physical, psychological, social, economic, legal, or
- where the research may present a legal risk to subjects through a loss of confidentiality, address the need for a *Certificate of Confidentiality* .

If other methods of research present fewer risks, Principal Investigators should describe those, if any, that were considered and why they will not be used.

Any potential for discomfort associated with any test or procedure performed for research purposes should be noted.

In general, risks to subjects must be minimized

- by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk and
- whenever appropriate, by using data and procedures already being performed on the subjects for diagnostic or treatment purposes.

For all research involving any risk of physical injury (including any adverse effect affecting the body, such as rashes and infections) these risks must be specified. If there are none, state: “There are no risks of physical injury.” However, if there are risks of physical injury, the protocol should state the potential injury, a careful estimate of its probability and severity, and its potential duration and the likelihood of its reversibility.

There should be a statement as to whether these risks are presented by:

- a procedure or modality performed or administered as part of standard care or
- a procedure or modality performed or administered solely as a result of the subjects participation in the research protocol.

Principal Investigators should specify:

- quantities of body fluids or tissues (*e.g.*, volume of blood, urine, saliva, number of biopsies),
- the time the subject will have to spend being tested, and
- the duration of the study.

Discussion of the risks should also include the risks of non-treatment.

If drugs or medical devices are being used which have known potential adverse side effects Principal Investigators should indicate if side effects are reversible.

Risks associated with a drug washout period, non-treatment or discontinuation of active drugs must be addressed by Principal Investigators.

Principal Investigators shall include a description of procedures (including confidentiality safeguards) for protecting against or minimizing injuries (physical, psychological and social) and provide an assessment of their likely effectiveness. There should be a clear statement about procedures for early detection of adverse effects and what steps, if any, will be taken to avoid injury to subjects, for example, the subject might be withdrawn from the study or a corrective drug might be administered.

Subject Recruitment

The Principal Investigator should indicate where subjects will be recruited (*e.g.* in patient unit, walk in clinic, emergency room, ICU, or outside of UVa). The Principal Investigator should also note whether normal controls are to be used and, if applicable, recruitment methods (*e.g.*, advertisements). The IRB reviews the information contained in advertisements and other subject recruitment material and the mode of its communication. The IRB also reviews the format of any Internet information and the final copy of printed advertisements to evaluate the relative size of type used and other visual effects.

Review Preparatory to Research and Recruitment

IRB-HSR review and approval is required prior to initiating research involving health information. Investigators are not authorized to contact potential research subjects identified in reviews preparatory to research unless they are directly responsible for care of the potential subject and entitled to PHI as a result of that duty.

NOTE: All recruitment materials must be approved by the IRB prior to use. Information about recruitment materials, IRB-HSR submission process, and templates are available on the IRB-HSR Website under Subject Selection, Recruitment and Compensation .

Subject Compensation/Reimbursement

It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug or device research or in behavioral and epidemiological research which require a significant time commitment on the part of the subject. The investigator should set forth the compensation plan in the

protocol. Plans which call for the entire payment being made at the completion of the protocol may appear to be coercive.
Subjects may also be reimbursed for out of pocket expenses related to participation (travel costs, parking expenses, child care, etc.) If such monetary compensation or reimbursement is to be offered, investigators should state the amount subjects are to receive. To view additional information on the difference between compensation and reimbursement click on "More Information". Researchers should be aware of the Compensation to Research Trial Participants Procedure from the Office of the Vice President for Research. The procedure requires the researcher to provide justification if compensation cannot be done via the UVa Oracle System or if the researcher is unable to obtain tax information such as name, address, and Social Security number of recipient of compensation. For additional info see:
Justification for use of an alternative method of compensation
Justification for not collecting the tax information

Study Management and Personnel

The Principal Investigator should name the professional staff who will be performing the study as sub-investigators, the research study coordinators, and other study support staff. Study staff must complete the UVA required CITI training program. Where tissue samples or data will be collected and stored, the Principal Investigator should indicate who will be responsible for storage, under what circumstances data or samples will be released, what future types of research are anticipated using the specimens or data, and what steps will be taken to protect confidentiality (*i.e.* , all identifiers stripped or, if coded, persons with access to code and location of code). Methods for protecting the security of information should be included.

If the study is a Phase I or Phase II clinical trial and provides for a Data and Safety Management Board, those provisions should be included in the Data and Safety Monitoring Plan

In long term studies, study management issues that the Principal Investigator should address are: the continuity of study personnel; availability of co-investigators; the timing of periodic review of data to assess trends; continuing training for data managers or study personnel to eliminate deviations from the protocol; and the investigator's plan, if any, to "re consent" subjects and obtain authorization over a number of years.

Confidentiality and Data Storage

When appropriate, the subject should be assured that steps will be taken to assure confidentiality. The Principal Investigator should explain how subject confidentiality will be preserved, how data will be kept confidential and used for professional purposes, and whether data will be coded and where the data will be kept (*i.e.*, in locked files). This is particularly important in studies in which information will be recorded which, in the view of the subject, is sufficiently sensitive so that he/she would not wish persons other than the investigators to have access to it. In such cases, data may be marked only with a code number and identifying information filed separately, with access to the code limited to responsible investigators. The protocol should also address any potential harm resulting. Whatever measures are taken to assure confidentiality should also be discussed in general terms in the consent form.

Special confidentiality requirements apply to different types of studies such as high risk genetics or HIV/AIDS research or research which may present a legal risk to subjects through a loss of confidentiality.

Certain research may qualify for additional privacy protection in the form of a Certificate of Confidentiality (federal funding is not required). Investigators may request a Certificate of Confidentiality to be issued by a Federal Agency when research is of a sensitive nature (*e.g.* involves information pertaining to illegal conduct or

relating to the use of alcohol or drugs, sexual attitudes, preferences or practices, mental health, or information potentially damaging to the subject's financial standing, employability or reputation) and the additional protection is judged necessary to achieve the research objectives.

Data Analysis and Evaluation Techniques

The Principal Investigator should describe the types of analyses to be performed and evaluation techniques (endpoints, pharmacodynamic assessments, outcome measurements, etc.). If the study entails the collection of body fluids or tissues, the analytical procedure to be followed should be presented and referenced (unless obvious). If a new technique that has not been documented in the literature is to be used, the Principal Investigator should describe the technique or include a statement about the method that will be developed. The Principal Investigator should indicate determinations of response to therapy. These may include laboratory assays, biopsies, bone marrow testing, absence of symptoms, or normal blood levels. The definition of partial response and failure should be included.

If the study is designed to evaluate behavior through the use of subjective or objective rating scales, or to study quality of life or activities of daily living, the method of evaluation should be explained with references.

If the study is designed to evaluate behavior through the use of subjective or objective rating scales, or to study quality of life or activities of daily living, the method of evaluation should be explained with references.
The description of the analytical and statistical techniques should be as explicit as possible. All manipulations of the data should be explained, and the statistical methods to be used should be identified. Simple statements about an "appropriate analytical technique" and an "appropriate statistical test" are discouraged; they imply that the investigator has not fully planned the study.

Bibliography

A reasonable list of references directly related to the study should be included.

Appendices

When additional information is needed to support decisions made by the Principal Investigator, it should be included in an appendix. Typically, appendices include such information as height and weight tables, a description of analytical methodology, calculations, subject screening criteria, subjective and objective rating scales and any supportive literature. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

INFORMED CONSENT

RESEARCH EXEMPT FROM INFORMED CONSENT

If the IRB determines that the research is exempt from IRB review, the research may not require a consent form. If, however, the research involves protected health information, the researcher must seek each subject's HIPAA authorization or obtain an IRB Waiver of Authorization , even if the research itself is exempt from IRB review.

WAIVER OF DOCUMENTATION OF INFORMED CONSENT

The federal regulations allow the IRB to waive the requirement for the Principal Investigator to obtain a signed consent form if it finds either:

- that the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; or
- that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

Principal Investigators may request a waiver of a signed consent document by indicating this request in the protocol. Under this type of an approval the researcher would still obtain a verbal approval from a potential subject to participate.

ALTERING OR WAIVING ELEMENTS OF INFORMED CONSENT/WAIVER OF CONSENT

For studies not under the FDA jurisdiction, the IRB may approve a consent procedure which omits or which alters some or all of the elements of informed consent. A Principal Investigator may request a waiver of one or more elements of informed consent by indicating this request to the IRB by identifying and explaining under which category the waiver is appropriate. Criteria which might allow the IRB to waive elements of informed consent include:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
   one or more of:

- public benefit or service programs; or
- procedures for obtaining benefits or services under those programs; or
- possible changes in or alternatives to those programs or procedures; or
- possible changes in methods or levels of payment for benefits or services under those programs and
- the research could not practicably be carried out without the waiver or alteration;

OR

2. The research meets all of the following criteria:

- involves no more than minimal risk to the subjects. The PI should describe the Risks of Harm to the subjects involved in the study and explain why the study involves no more than minimal risk to the subjects. (Minimal risk means that the probability and magnitude of harm are not greater than those ordinarily encountered in daily life or during routine examinations of the general population.) The IRB will determine whether a risk is minimal.
- the waiver or alteration will not adversely affect the rights and welfare of the subjects.
- the research could not practicably be carried out without the waiver or alteration. “Impracticable” is not an inconvenience or increase in time or expense to the investigator or investigation, but rather it is for instances in which the additional cost would make the research prohibitively expensive or where the identification and contact of thousands of potential subjects, while not impossible, may not be feasible for the anticipated results of the study.

Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The IRB carefully reviews such requests and determines whether alteration or waiver is appropriate and permissible in each situation.

The Privacy Rule also permits the IRB to alter the required form of authorization, if the IRB makes a separate set of findings and determines that the waiver criteria contained in the privacy rule are satisfied.

ELEMENTS OF CONSENT FORM

The consent form must include:

- **A statement that the study involves research**. The statement that the study involves research is particularly important for clinical research because the relationship between patient-physician is different than that between subject-investigator.
- **Purpose of the research**. It should be clear to the subject that this is research. This section should include the rationale for the research that is being conducted and the specific purposes for the proposed research. Consent documents for studies of investigational articles (drugs, biologics or devices) should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that indicate test articles are safe or statements that the safety has been established in other studies are not appropriate when the purpose of the study includes the determination of safety. Studies that involve efficacy should also include the effectiveness of the test article, as a study purpose, but should not make claims of effectiveness.
- **Procedures**. The subject must be informed exactly what his or her participation will involve, with particular attention to the way it will be experienced by the subject. This should include the length of time and frequency of each procedure (*e.g.*, hospitalizations, visits to the investigator, types of medication, drug dosages, types and numbers of tests, amount of blood to be withdrawn, questionnaires, videotaping, diets, withholding of standard treatment, and follow up studies), as well as the overall length of time a subject is expected to participate. It should be made clear which of these procedures are being done in the interests of research and which are being done to provide diagnosis, prevention, or therapy. Of the various diagnostic maneuvers (*e.g.*, laboratory tests) the consent form should specify which are extra in that they would not have been done during customary therapy or would not have been done as often. The approximate number of subjects to be involved in the study should also be included.
- **Risks or discomforts** to the subject. These include not only physical injury, but also possible psychological, social or economic harm, discomfort or inconvenience. These may include side effects of drugs, hazards of procedures, or dangers of withholding a therapy of proven value. The subject should be told what will be done to minimize risks and counteract side effects and which, if any, side effects might be irreversible. In addition to the known risks of being in the study, there may be unforeseeable complications; the subject should be made aware of this fact.
- **Benefits of the research** to the subject. If there is no expectation of direct benefit to the subject (treatment and non-treatment arms must be considered), state that clearly. **It is highly encouraged that spell-check/grammar check is used on your consent form(s) prior to submitting to the IRB.** It should be made clear whether the subject will be offered continuing access to an investigational therapy after completion of the study; if so, whether it will be provided free or whether the subject will be expected to pay for it.
- **Treatment Alternatives**. The consent form must identify the subject's alternatives to participation in the protocol and should offer a discussion of their relative advantages and disadvantages. It is usually

not necessary to provide a full account of the risks and benefits of alternative treatments in the research consent form. In some cases it may be appropriate to state that one reasonable alternative for the prospective subject is to choose no therapy.

- **Costs of Participation**. The financial consequences to the subject of participation in the project should be stated clearly. This includes disclosure of insurance co-payment obligations for services that will be billed to third-party payers as well as a subject's liability for costs not covered by a sponsor, insurer, or the provider. Third-party payers cannot be billed for procedures performed purely for research purposes. If the research treatment or procedure is not covered by Medicare, Medicaid, third-party insurers or the research sponsor, the subject may be responsible for payment. In such case, state which treatments or procedures are not likely to be covered by third-party payers and the approximate charge for each.
- **Confidentiality**. Steps taken to assure confidentiality should be explained in the consent form. The subject should be informed about the disposition of information obtained during a study. Limits on confidentiality, such as inspection of medical records by the IRB or agents of the FDA, and the industrial sponsor in studies involving investigational drugs and devices, should also be explained. Subjects should be informed about information that will be included in the subject's medical record. If the study events are not directly related to diagnosis or therapy, the subject may decide whether or not such information shall be entered into a medical record, transmitted directly to a private physician or retained only in the Study record.
- **Voluntary Participation**. The consent form must state that participation is voluntary and that refusal to participate will not result in any penalty or any loss of benefits that the person is otherwise entitled to receive. Subjects should be informed that they are free to decide whether or not to participate, and also free to withdraw from the study at any time unless the nature of the investigation, once commenced, precludes this. They should be assured that if they prefer not to participate or decide to withdraw, they will still receive standard treatment, if such a statement is appropriate. There should also be assurance that a decision not to participate will not adversely prejudice future interactions with the institution. This is particularly important when a dependent relationship exists between the investigator and the subject, such as physician-subject, employer-employee or faculty-student. If withdrawal or non-participation in the study would result in transfer of the subject to another service or institution, this must be made clear.
- **Right to Withdraw**. A subject's right to withdraw from the study at any time without penalty, including without loss of credit or of financial reward for the work completed should be included. The right to withdraw includes the right to require that stored tissue specimens be destroyed or anonymized. When appropriate, it may be necessary that a consent form includes the consequences of a subject's decision to withdraw from the research and the procedures for the safe and orderly termination of participation by the subject. In some studies, abrupt withdrawal from a study may be dangerous to a subject. In such cases, this danger must be explained and it must be made clear that the subject should not withdraw without first discussing it with the investigator.
- **HIPAA**: Covered entities may continue to use and disclose protected health information that was obtained prior to the time the individual revoked his or her authorization, as necessary to maintain the integrity of the research study. Additional information may be found in 45 CFR 164.508(b)(5)(i).However, the reliance exception would not permit a covered entity to continue disclosing additional protected health information to a researcher or to use for its own research purposes information not already gathered at the time an individual withdraws his or her authorization.
- **Termination of Participation**. The consent form must include anticipated circumstances under which the subject's participation may be terminated by the Principal Investigator without regard to the subject's consent.
- **Compensation for Subject Injury**.. It is acceptable to include information on a sponsor's policy regarding compensation for injury in addition to the UVA policy as stated in the consent form template.

The sponsor's policy regarding compensation for adverse events/ subject injury should reflect the compensation/subject injury terms appearing in the contract between the sponsor and UVA.

- **Significant New Findings**. The form must include a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (All such information must also be provided to and retained by the IRB in its records.)
- **Conflict of Interest**. Principal Investigators must disclose to potential subjects any conflict that they have with the sponsor or in the research for which the subjects are being recruited, including capitation payments, bonuses or other incentives paid by the sponsor for enrollment (as opposed to reasonable payments for necessary study services) and any other personal conflict deemed necessary by the IRB.
- **Questions**. The subjects and/or parents or guardians should be encouraged to ask questions. If the proposed procedures are complex or involve considerable risk, there should be adequate time provided for subjects to discuss their decision with their own physician or other respected persons before making a decision. Principal Investigators should be as certain as possible that subjects understand the purpose, the procedures involved, the risks and the benefits, if any, of participating in the study.
- **Continuing Contact**. The consent form should include the name and telephone number of a person to contact for answers to questions and a person to contact in the event of a research-related injury or emergency. The name and telephone number of the Principal Investigator and the IRB office address and telephone number should be specified.
- **Signatures**. Spaces should be provided for the signature of the person who consents to participate in the study or the legally authorized representative who consents on behalf of the individual who will be the subject of the study. There should also be a space also for the signature of the person who obtains the consent -- the Principal Investigator or the authorized representative. If the subject is a child or is legally incompetent, such subject may indicate her or his assent by signing the consent or assent form, depending on age of the child, after the procedures have been explained (unless otherwise determined by the IRB). Assent of the child subject may also be obtained verbally. In this case, the IRB requires the signature of the person obtaining verbal assent from the child to be present on the consent form.
- **Version Date/Page Numbering**. Each page of the consent form should be numbered and should contain the current version date. Each time the consent form is revised , the version date should be changed accordingly.

Purpose of Consent Process and Documentation

Informed consent is understood as an on-going process which starts with the initial presentation of a research activity to a prospective subject by the investigator and continues through the research activity until the subject ends his/her participation or the study closes. Research subjects are rarely aware of research activities prior to an initial presentation by the principal investigator or a member of a principal investigator's research team. The initial phase of consent requesting participation in a research activity commonly begins with the first contact between the subject and the investigator. Many subjects make their decision regarding whether to participate in research during this initial contact. As a result, the greatest potential for misunderstanding exists in the initial consent process. Researchers must provide sufficient time for a potential subject to reflect on the nature of participation during the important initial presentation of a research activity. When subjects are presented with numerous research and clinical options, the consent process must include a clear description of the possible known ramifications resulting from each option presented. Subjects must also be made aware of the possibility of unforeseen risks resulting from participation in the research project. The presentation must not include specific "leading" information about whether to participate in any particular project.

By providing a potential subject with information understandable to the subject in an initial session regarding complex research issues, potential subjects should have an improved comprehension of the elements within the consent form and provide a more informed consent for participation in the research.

The second step in the consent process is the presentation of the consent forms to the subject. In biomedical research the investigator should separate the research consent form from any other clinical information or hospital admission forms. Subjects should not be asked to sign hospital admission paperwork or hospital consent documents for clinically indicated procedures at the same time as the presentation of the research consent form. Individuals who have already received pre-op medication or anesthesia should not be asked to sign a consent to participate in human research. The presentation of the research consent form should be a separate process. The principal investigator or a member of the research team should ensure that the subject or legally authorized representative (LAR) reads the consent form or has it read to them. After the subject or LAR reads the consent form or has it read to them, the principal investigator or member of the research team should ask the subject or LAR if he/she has any questions regarding the information contained in the consent form. **Please note that the IRB must approve the use of an LAR or surrogate prior to obtaining their assent.**

Assessing Subject's Understanding

In situations where the ability of the subject to understand the form is in question, for example, the subject is possibly educationally or mentally challenged, the investigator or member of the research team may wish to ask questions of the subject to ensure an understanding of the basic elements of the consent form. In performing an assessment of the subject's comprehension of the consent form, an investigator should request that the subject indicate the risks of participation, how the subject may withdraw, and what alternatives exist to participation in the research. The decision-making capacity of subjects with psychiatric disorders or cognitive deficits (such as dementia) should be evaluated by a practitioner with expertise in the area.

All efforts should be made to offer the potential subject or LAR sufficient time to consider the information contained in the consent form. The potential subject or LAR should be given the opportunity to take the consent form home and sign the form on a return visit or be left alone to consult about enrollment with family or friends. If the individual decides to participate, he/she is asked to sign the consent form. The person obtaining the subject's informed consent must also sign the form. The subject must be given a copy of the form the subject signed. The FDA (drug or device studies) explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. The original consent is retained in the investigator's files.

General Principles

The consent form should be a statement addressed to the subject that gives reasonable information about the study, its procedures, benefits, risks, and alternatives, to enable him/her to make an intelligent decision about participation. The consent form should be written in a language and level which the prospective subject can be expected to understand. It should be concise, literate and be proofread carefully for errors in spelling and grammar.

The consent form must not be overly encouraging or coercive. It may not include any language through which a subject is made to waive or to appear to waive any legal rights or to release the institution or its agents from liability for negligence.

All subjects invited to participate in a research protocol must be given the opportunity for informed consent or refusal. For these purposes, control subjects are always viewed in the same way as other subjects, even if the research plan is to treat control subjects with standard accepted diagnostic and therapeutic maneuvers.

Standardized research consent forms have been developed by the IRB which indicate the elements of informed consent required by the federal regulations and require the Principal Investigator to insert the study-specific information.

If a procedure is performed solely for purposes of identifying a population of future research subjects, consent is required. Investigators may wish to present prospective subjects with a consent form describing only this procedure and stating as its purpose a determination as to whether the subjects will be eligible for participation in further studies. If the screening involves access to, or creation of, prospective subjects' protected health information, a HIPAA authorization will also be required. A separate consent/authorization form may then be presented to those who are found to be suitable. In such situations, while soliciting consent to the qualifying tests, the Principal Investigator is expected to show potential subjects the consent/authorization form they will be asked to sign if they prove to be suitable subjects for further study.

It is highly encouraged that spell-check/grammar check is used on your consent form(s) prior to submitting to the IRB.

The consent form signed by the subject in the original must be kept in the study files. A copy of the signed consent form must be given to the subject. If the research involves protected health information, a HIPPA authorization is required. At UVa, the HIPAA authorization is combined with the research consent form.

If there are two or more consent forms, each should be clearly labeled as to which subject population is addressed (*i.e.*, subject/ subjects, normal controls, family members). Type must be clear and readily legible, in standard size, which is 10 to 12 points. Twelve (12) point-type is preferred.

Principal Investigators may not make any changes to the text of the informed consent and authorization form approved by the IRB without the IRB's prior written approval. In cases where a Principal Investigator is requested to change the text of the informed consent documentation by other third parties, the revised informed consent document must be resubmitted to the IRB for approval prior to initiating the study.

If **videotapes** are to be made for research purposes, the consent form should state when the tape will be erased, that the subject has the right to demand erasure at any time, and the circumstances, if any, under which the tape might be used for purposes other than the research described in the protocol (*e.g.*, educational purposes).
It is the policy of the IRB that the consent process shall be conducted by the investigator or other professional staff listed on the protocol that are knowledgeable about the protocol.

Understandable Language

The primary goal of a consent form is to provide all required information about a study in language and format that is comprehensible to the subject population. Everyday vocabulary and simple sentence structure should be used throughout the form. While Principal Investigators always have the option of describing the study in more detail during the consent process itself, the written description of the study should be simple and straightforward so that subjects will have a consent form to take home with them and refer to over the course of their

participation in the study. Unless the subjects are themselves medical professionals, scientific or technical terms should either be replaced with or defined in lay language.

For example, "blood draw" is preferable to "venipuncture," "X ray" to "radiographs", "upset stomach" to "GI upset," "obstruction" to "occlusion". A list of technical terms and lay language for lab tests can be obtained from links on the IRB-HSR website. Legalistic sounding language such as "you hereby agree", "you certify that", "you the undersigned, do acknowledge that" should not be used. Phrases similar to the following should be: "you have been told that", "It has been explained to you that". These phrases do not assure a subject's comprehension and lend the appearance of a legal document to the consent form.

Some useful tips in making a consent more readable include:

- Using short sentences
- Using works with a lower number of syllables

Person of the Form

The person-tense in which the form is written should be consistent throughout the form. The second person (*i.e.*, "you are being asked") is preferable, but not required.

Who can obtain consent from potential subjects?

Ultimately, the responsibility of who can obtain consent rests with the PI. However, only those individuals listed on the protocol with the IRB can obtain consent. All key personnel, including a study team member who obtains consent from a subject must complete the mandatory IRB-CITI training. For additional information see:CITI Training.

INFORMED CONSENT CONSIDERATIONS FOR CERTAIN TYPES OF STUDIES

Certain types of studies have special and important informed consent considerations. These are **in addition** to those considerations already discussed and the Principal Investigators should consider all of these elements when preparing a consent form.

Deception Trials

The nature of some studies requires that the full purpose not be revealed to the subject until the study is completed. Such deliberate withholding of information is permitted only if the subject is informed that this is the case and agrees. This must be clearly stated in the consent form, along with the plan for when and how the complete information will be shared with the subject. Research based on deception or incomplete disclosure should be thoroughly justified and discussed with the IRB reviewer assigned to primary review of the study.

Drug Trials

The informed consent document for drug trials must ensure that subjects understand that the drug is investigational, that its benefits for the condition are unproven, and, if applicable, that the physician/ investigator may have a potential conflict of interest. In Phase 1 trials, subjects must understand that the primary purpose of Phase 1 trials is generally to determine safety and pharmacy of the drug rather than provide a direct benefit to subjects.

Principal Investigators should use the generic/pharmacological name(s) of the agents, not the trade name(s). This also applies to the names of drug(s) used in the title of the project. The dose/dosage range of drugs to be administered must be clearly stated in the consent form. Availability of experimental drug(s) to the subject following the end of the subjects' participation and/or the close of the study and how the cost will be covered must also be clearly stated.

Epidemiologic Studies

In epidemiologic studies, the IRB requires that the information provided to prospective subjects include descriptions of the kind of data that will be collected, the identity of the persons who will have access to the data, the safeguards that will be used to protect the data from inappropriate disclosure, the risks that could result from disclosure, whether identifiers will be collected, and whether they will be contacted again in the future. In long term studies, the IRB asks Principal Investigators to present a plan to obtain continuing consent from subjects at critical intervals (*e.g.*, where the protocol is altered, new information becomes available). The initial consent at the beginning of a study usually will not suffice over an extended period of time.

Genetic Research

Principal Investigators conducting genetic research must submit a proposed consent form that addresses these issues and should also discuss the following issues in the protocol, as applicable.

1. If **children** are directly involved (*e.g.*, with blood draws, biopsies, interviews), whether they will benefit directly from participating in the project.
2. If **extended family members** are involved: (a) how they will be contacted and recruited in a way that does not unduly influence or coerce them to participate; (b) whether there are confidentiality issues involved (*e.g.*, extended family members may not know an individual is sick or has a specific condition) and, if so, how they will be handled; and, (c) what measures can be taken to minimize family pressure on children in the extended family to participate.
3. What **information families will receive** at what point in the research and the meaning of the information, *e.g.*, diagnostic, predictive, or reproductive implications. How interim or inconclusive results will be handled. Many genetic studies will not yield information that will be clinical useful to the subjects for some time.
4. If some **information may be given to each subject**, state what information subjects will receive and when during the study. For example, will test information be conveyed separately to each subject upon receiving results, or only after the study is completed. Indicate if this information will represent only that which pertains to each subject or if it will be aggregate data from all study subjects.
5. Whether **subjects or family members will be given the choice to receive or not to receive** study information or information about themselves. If they will have that choice, an option for noting their choice must be in the consent.
6. Whether there are **psychological risks** (*e.g.*, anxiety, confusion) associated with the research and the results obtained. If so, an explanation of how the information will be given to families in a way that will minimize these risks and the supports available to the subjects after they receive the information, *i.e.*, genetic counseling. If children are directly involved in the project, an explanation of how the data will be gathered and conveyed to them in a way that minimizes self-doubt and anxiety.
7. Whether there are **social risks** (*e.g.*, jeopardy to insurability, employability, damage to familial relationships) associated with the research and the results obtained. If so, how the research data will be protected from third parties, such as employers and insurance companies, and steps that the subjects should take to assure that potential economic risks are minimized. If extended family members are to be studied, what methods will be used to protect family members from unauthorized disclosure of medical or other personal information about themselves to other family members?

8. State the **possible clinical implications** of receiving the test results. If appropriate, include the level of certainty that a positive test result serves as a predictor of the disease being studied.
9. Whether there is a possibility of **incidental findings**, such as paternity or information about diseases or conditions other than the one(s) under study, and, if so, an explanation of how this information will be handled.
10. An explanation of **whether research findings will be disclosed** to the subject's physician for **clinical use**. If they will have that choice, an option for specific consent for this must be included with a location to note their choice in the consent form.
11. An explanation of how **data/samples will be handled**: (a) if a subject wishes to withdraw from a genetic study after it has begun; (b) if a subject wishes to withdraw from a genetic study after the project has been completed; and (c) if either the current Principal Investigator or another investigator wishes to use the research data/samples from this project for different research purposes.
12. An explanation of **whether or not personal identifiers will be maintained** with the tissue or DNA specimens or not, recorded as part of the study records, or if links to personal identifiers will be maintained in a master list. Describe what personal identifiers will be recorded, such as name, medical record number, social security number or other code. Describe whether or not a subject would be re-contacted and given information from the specimens. If so, under what circumstances.

HIV/AIDS Related Research

Principal Investigators should ensure that study information that identifies the subject is not disclosed without the subject's consent. Principal Investigators should consider whether additional safeguards are necessary when research involves subjects in the later stages of the HIV-related illness, since the illness can cause dementia. Principal Investigators should also ensure that there is a mechanism for dealing with changes in mental capacity and continuing consent, if necessary.

Ionizing Radiation

If your study involves a single X-ray procedure for which standard wording is provided by the RSC the researcher may use the exact wording provided. The consent form will not need to be reviewed by the Radiation Safety Committee subcommittee (HIRE – Human Investigations Involving Radiation Exposure). You must however, send them an electronic copy of the protocol and consent form(s) after the study is approved by the IRB.

If the researcher not using a single procedure- you must obtain approval from the RSC prior to being allowed to enroll subjects. The researcher must provide their approval to the IRB-HSR.

Randomized Trials and Placebos

For randomized trials, the consent form should state the fact that subjects may be kept unaware of their treatment assignments in "blinded" studies and research involving placebos. Ethical considerations demand that subjects be informed when their assignment will be random, the percent chance they have of receiving both the experimental therapy and the alternative treatment, and that one of the possible consequences of participation is that the group to which they are assigned may receive the less effective intervention. Further, subjects should be told who will know whether they are receiving the placebo or the active agent. In a double-blinded trial, for example, subjects should be told that neither they nor the Principal Investigator will know whether they are receiving the placebo or the experimental therapy.

In studies involving a placebo washout, subjects should be told that at some point during the study all subjects will receive placebo treatment; Principal Investigators but not subjects will know when subjects are receiving placebos for washout purposes.

Use of Biological Specimens and Specimen Banking

Types of Human Biological Specimens

Most human biological specimens come from samples collected for diagnostic or therapeutic procedures, but other sources can include autopsies, volunteer donors, or materials collected and shared by other researchers.

- The term "biospecimen" is used widely and encompasses a full range of human specimen types including:

  - Sub-cellular components such as DNA or RNA
  - Cells or tissues from any part of the human body
  - Organs such as liver, bladder, kidney, heart, placenta, etc.
  - Gametes (ova and sperm)
  - Embryos and fetal tissues
  - Breast milk
  - Exhaled air
  - Bodily products such as teeth, hair, nail clippings, sweat, urine, feces
  - Blood and blood fractions: plasma, serum, buffy coat, red blood cells
  - Saliva and buccal cells

- Exceptions: Organisms, such as bacteria and viruses, isolated from human specimens are not human biological specimens.

Specimen Banks and Repositories

Various terms are used to designate the storage sites for human biological collections. The most common are defined below.

- **Repository** is a term usually applied to large formal collections of specimens and/or data. Examples include:
  - The National Pathology Repository
  - The Cooperative Human Tissue Network
- **Specimen bank** generally refers to smaller collections of specimens, which may be specific to an institution, disease, or even to specimens in a researcher's freezer.

Approvals Needed to Collect and/or Bank Human Specimens

If the researcher is involved in collecting specimens from research subjects or intend to receive specimens from clinicians for banking purposes, the researcher will need to obtain protocol approval from the IRB.

Specimen Sources

- **Federally funded or cooperative group banks** usually have well-defined prioritization and distribution methods. Be prepared to provide a Letter of Intent (LOI) or a study protocol describing your research plan. Applications are generally reviewed by an oversight committee and judged on scientific merit, statistical validity, the investigator's ability to conduct the proposed research, and the appropriateness of the sample size requested to accomplish the research goals.

- **Departmental/Division banks and investigator-maintained collections** may not have well-established application or distribution policies and may not be obligated to share specimen resources at all. Contact the tissue bank's administrator to find out how to obtain specimens.
- **Commercial Tissue Banks:** Specimens may be available for purchase from commercial sources.
- **Private Collections:** Individual researchers who are collecting specimens in your area of research may be willing to provide them. Contact the researcher directly to find out if collaboration is an option and the conditions for transferring or sharing specimens.

Informed Consent Issues

The informed consent form for the collection of biological specimens should ask subjects whether:

- the tissue may be kept for use in research to learn about, prevent, treat or cure a particular disease;
- the tissue may be kept for research about other health problems and
- if someone from UVa may contact the subject in the future to ask him/her to take part in more research.

The consent should also obtain a description of:

- whether tissue specimens will be stored for future research, maintained in a repository or used to establish a cell line, or otherwise how the DNA information from tissue specimens will be utilized in this study.
- where the tissue specimens will be stored; specify the location within the hospital or outside of the hospital.
- the purpose of storing the tissue
- what types of research you or others might use these specimens for in the future.
- who will have access to the DNA information from tissue specimens collected
- who will control distribution of the tissue
- what will happen to stored specimens if the Principal Investigator leaves the present institution.
- an explanation of whether or not personal identifiers will be maintained with the tissue or DNA specimens or not, recorded as part of the study records, or if links to personal identifiers will be maintained in a master list.
- what personal identifiers will be recorded, such as name, medical record number, social security number or other code.
- whether or not a subject would be re-contacted and given information from the banked specimens. If so, under what circumstances.
- what will be done with the study specimens at any point during the study in the event of a subject's withdrawal (*e.g.*, the entire specimen/cell line could be removed from the study, identifiers could be removed, or information from the aggregate of study data already generated by a particular specimen could be removed).

CONSENTING SUBJECTS WHO DO NOT READ, SPEAK OR UNDERSTAND ENGLISH

The purpose of this section is to explain how researchers should obtain and document informed consent for subjects who:

- Are non-English speakers and require an interpreter and translated consent materials, or
- Understand English but cannot read due to blindness or illiteracy, or
- Understand English but cannot talk or write due to incapacitation.

The governing principles of human subject research: **respect for persons, beneficence, and justice,** require that researchers not exclude subjects based solely on their inability to read, speak or understand English. Investigators need either to communicate directly with subjects, or to provide a reliable alternative to ensure that:

- Study participation is **voluntary**, as indicated by free and truly informed consent (respect for persons); and
- Study **schedules, procedures, and risks are accurately communicated**, and subjects have ongoing opportunities to express concerns and ask questions, in order to minimize risks to subjects (beneficence); and
- There are fair **procedures and outcomes in the selection of research subjects** so that risks and benefits of research are shared in society *(justice)*.

Federal regulations enforced by the Office for Human Research Protections (45 CFR 46.116) and the Food and Drug Administration (21 CFR 50.20) state that informed consent "shall be in language understandable to the subject or the representative," and 45 CFR 46.117, along with 21 CFR 50.27 describe how the informed consent is to be documented.

Subjects who speak another language but do not read, speak or understand English

There are two methods for obtaining and documenting informed consent for research subjects who do not read, speak, or understand English:

1. The **preferred method** is to provide consent forms written in the subject's language.
2. For the occasional and unanticipated non-English-speaking subject, an **alternative "short form" method** is allowed [21 CFR 50.27(b)(2) and 45 CFR 46.117(b)(2)].

Informed consent is an ongoing process throughout a study. For non-English speakers, the investigator should address the means for providing continued, qualified interpretive services. Likewise, for those who understand English but cannot read, talk, or write, the investigator should be prepared to provide the necessary support to ensure the subject's ongoing comprehension of new information that may become available during the study.

Legally blind or illiterate subjects

If subjects who cannot read the consent materials due to illiteracy, blindness, or the subject's surrogate is legally blind, the following consent process is recommended:

- Have an impartial witness observe the consent process, such as a subject advocate or someone not affiliated with the research team. Family members are not recommended to serve as witnesses.
- The consent forms should be presented to potential subjects orally and the potential subject. You may wish to provide the subject with an audiotape of the discussion for their reference.
- If potential subjects have access to equipment that can read the consent document for them, provide them sufficient time to review the consent document independently of the research team.
- As would be expected for any consent process, ensure sufficient time is allowed for questions to be asked by the potential subject, subject's surrogate to ensure that the consent process was clear and effective.

- Add a statement to the consent form that the subject was unable to read the consent form and that they were read to the subject by a member of the research team designated to obtain informed consent.
- The subject signs and dates the consent form, if capable of doing so. In the case that informed consent is being obtained from the subject's surrogate the surrogate will instead sign and date the form.
- The witness signs and dates the consent form. A statement should precede the witness' signature that attests that the consent information was explained and that the subject apparently understood the information, and informed consent was given freely.

Ethical and Legal Considerations

As part of each consent discussion, investigators have an ethical and legal obligation to assess the subject's understanding of the consent information to ensure that the consent is truly "informed." When the investigator and subject do not share a language, the investigator must depend on the accuracy of the translated consent documents and the working relationship with the medical interpreter. The investigator's familiarity with the subject's culture ("cultural competency") or lack of familiarity affects the communication.

Clinical Investigations and Biomedical Studies

The medical and technical information discussed during the initial consent discussion, as well as ongoing, study-related information, can be very complex and should be communicated to non-English speaking-subjects **through an interpreter with training and understanding in medical terminology**. In addition, an individual with a professional commitment to maintain strict confidentiality should handle the private medical issues discussed with subjects.

Working Effectively with Medical Interpreters: The field of medical interpretation is evolving and although protocols are being developed, standardized practices do not exist. Investigators may want to discuss some or all of the following topics with the interpreter before participating in an interpreter-mediated consent discussion.

- If the English version of the consent form is orally interpreted for the alternative "short form" method, how will the interpreter incorporate cultural considerations into the consent information?
- How transparent will the interpreted conversation be? With three people communicating (subject, investigator and interpreter), will everything said by each person be translated?
- How will the investigator and interpreter determine whether the subject truly understands the consent information?
- Informed consent is an ongoing process. How will the investigator ensure that the subject will understand ongoing study-related communication? If the subject has questions about continuing in the study, how will that be communicated to the researchers?

Anticipating the Need for Written Translations:

As part of the IRB application process, investigators should estimate the likely proportions of non-English-speaking-people who may be encountered as eligible subjects for a proposed study.

Cost of Translation:

The cost of translating written consents is the investigator's responsibility. These costs may be quite high, particularly for large studies where multiple translations are needed and/or studies with relatively complex consent information that may require additional time by a skilled professional. Investigators should include the costs of written translations as well as medical interpreter services on grants and contracts. Industry sponsors are often willing to pay the costs of translating consent forms.

The IRB must receive and approve all foreign language versions of the short form document and any other translated documents presented to the subjects. Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

If a Principal Investigator wishes to include a subject who happens to be illiterate or if no translated consent document in the subject's language is reasonably available, then appropriate arrangements must be made to obtain verbal consent. Illiterate persons who understand English may have the consent read to them and make a "mark" on the subject signature line. Signatures of the person conducting the consent interview are required in such situations.

Translation Requirements:

The IRB will accept documents translated by an individual fluent (i.e., can speak, read and write) in a given language.

Differences between an interpretation and a translation: For purposes of research informed consent, an interpretation is a verbal exchange between two parties and the person serving as interpreter is fluent (can speak, read and write) in English and the language of the subject. A translation is the process of translating a written document (e.g., consent form) from one language into another, assuring the language of the translated document has the same meaning as the written document in the first language.

CONSENTING VULNERABLE SUBJECTS

Children

See: Special Consideration for Projects Involving Vulnerable Populations: Children

Cognitively Impaired Persons

See: Special Consideration for Projects Involving Vulnerable Populations: Cognitively Impaired Persons

RE-CONSENTING REQUIREMENTS

Research is an on-going process which involves the constant re-evaluation of current information and procedures. Therefore, investigators are ethically obligated to keep subjects apprized of all issues related to their participation in the study. New information should be presented to research subjects in a written form and the subjects should be asked to sign a copy of the form or to sign a revised consent form or addendum.

Federal regulations do not require re-consenting of subjects who have completed their active participation in the study, or of subjects who are still actively participating, when the proposed change will not affect their participation. However, when changes do occur in the conditions or the procedures of a study that would affect an individual subject, the investigator should once again seek informed consent from the subjects. Those subjects who are presently enrolled and actively participating in the study should be informed of the change and

re-consented if it might relate to the subjects' willingness to continue their participation in the study. Adverse events may occur during a research activity that would directly affect whether prospective or enrolled subjects would wish to continue in a particular research activity. The IRB also does not require a subject re-consent at the time of the protocol continuation approval, unless there have been modifications to the consent form that would affect an individual subject.

Investigators should note that the IRB requires IRB review and approval prior to an investigator providing subjects with any new research information.

Information also may arise regarding the study which should be shared with previously enrolled subjects after the completion of a study, or a specific treatment or procedure. For example, dysfunctional families may participate in qualitative research examining parenting techniques. Following data analysis, the investigator finds that a specific technique is superior to the other study arms of the project. As agents of a health care and educational institution, investigators are ethically obligated to provide this valuable new information to research participants.

It is difficult to be confident that volunteers truly understand the nature of their participation in research when they are confronted with volumes of complex scientific details in a brief and isolated session. Creating an on-going consent process will facilitate an exchange of information between subjects and investigators in a scientific environment of increasing complexity. By providing subjects with the opportunity to give effective and on-going informed consent in a process that incorporates the free exchange of information between both the researcher and the subject, investigators will continue to set standards for the conduct of ethical research.

Re-Consenting Subjects Who Are Cognitively Impaired

Consenting is an ongoing process. All applicable criteria that would trigger re-consenting a subject in any study shall apply to subjects whose consent has been provided by a LAR. In addition:

- A subject who regains the cognitive ability to consent as determined by the PI, must be re-consented using standard consenting procedures.
- In the event a subject has been initially consented by a LAR, and a LAR of higher priority subsequently notifies the investigator of that relationship to the subject, the investigator must defer to the higher priority LAR's decision regarding whether the subject will continue to participate or to withdraw from the study.
- Investigators shall describe to potential LARs the nature of ongoing decisions during the study regarding the subject's participation, decision to participate in certain procedures, changes to the study, etc., in order to ensure that the LAR will be willing to undertake these on-going responsibilities.
- In the event that the LAR dies, the subject must be re-consented subsequently upon any event that would otherwise trigger re-consenting the subject.

TYPES OF SUBMISSIONS TO THE IRB

New Protocols

Investigators are required to obtain a prospective IRB review and approval if any of the following criteria exist:

- When research with human subjects is conducted by an employee, student or agent, or under the direction of an employee or agent of University of Virginia, or its affiliated institutions, in connection with his or her institutional responsibilities, or
- When the conduct or recruitment of the research involves institutional resources (property), facilities or funding, including extramural funds administered by University of Virginia, or
- When the research involves the use of University of Virginia's nonpublic information to identify or contact human research subjects or prospective subjects.
- For details on how to submit a protocol application see IRB-HSR Protocol Submission Process.

Submission of a Protocol to a Second IRB after Disapproval from another IRB

If an investigator submits a protocol to a University of Virginia IRB or to another IRB outside the University and the reviewing IRB disapproves the study, and it is subsequently sent to another IRB for review, that IRB must be informed by the PI of the original disapproval.

When an IRB disapproves a study, it must provide a written statement of the reasons for its decision to the investigator and the institution. If the study is submitted to a second IRB, a copy of this written statement should be included with the study documentation so that it can make an informed decision about the study. Federal regulations require an IRB to "... review ... all research activities...." The FDA regulations do not prohibit submission of a study to another IRB following disapproval. However, all pertinent information about the study should be provided to the second IRB.

Grant Application for Non-industry Sponsored Research

Where a protocol has funding from a grant and the proposal involves the use of human subjects in research, a copy of the grant proposal must be forwarded to the IRB along with all other documentation. No work may be initiated on a grant or protocols funded by that grant prior to receipt of approval from the IRB. For details on how to submit a grant application see IRB-HSR Grant Submission Process.

Instruments

The IRB is required to review all research instruments including standardized instruments such as surveys, questionnaires, inventories and assessments to be used in the proposed research. Please include the instruments, if available, with your initial application. Investigators may submit draft versions of investigator initiated study instruments for the IRB to review. The IRB is required to review any modifications to research instruments. Please submit a modification to the IRB when requesting changes to previously approved instruments. If draft instruments are submitted, the instruments cannot be used until they are approved by the IRB.

Investigators Transferring Protocols/ Grants From Outside Institution

Investigators who transfer research to University of Virginia from their previous institution are required to submit the protocols/grants to the IRB for review and approval in order to continue the study.

Please feel free to contact the IRB's for further information. See IRB Contacts.
Which IRB should I submit to?
IRB-HSR Protocol Submission Procedures
IRB-HSR Grant Submission Procedures

Submissions Required After Initial Protocol Approval

For information on submissions required after initial protocol approval see: Maintaining a Protocol After Initial Approval

Review of Human Subjects Research Activities by Other University Committees/Offices

Investigators must submit other required institutional review committee approvals (Conflict of Interest Committee, Institutional Biosafety Committee, Radiation Safety Committee, General Clinical Research Center Advisory Committee, Protocol Review Committee etc.) to the IRB.

Though other institutional committees share the responsibility for following guidelines in our collective effort to protect human subjects, ultimately the final authority for participation of human subjects in research falls on the IRB.

Researchers must obtain approval from PRC prior to the protocol being submitted to the IRB. Researchers are not required to wait for the approval of the other UVA institutional review committees before submitting a proposal to the IRB. However, the researcher will not be allowed to enroll subjects until the investigator forwards documentation of approvals from other institutional review committees to the IRB. At that time, the modification will be reviewed and the researcher will be sent notification that they may begin enrollment.

UVA Conflict of Interest Committee

The Conflict of Interest Committee for Management of Investigator Financial Interests in Research (COI). The University of Virginia Vice President for Research appoints a COI committee and chair that operates administratively under the AVPR. The COI is made up of faculty members from the various schools at the University, senior administrators, an IRB member, and a non-affiliated community member, representing diversity of expertise needed to adequately review potential conflicts of interest. This committee reviews cases in which an investigator holds a significant financial interest that may affect or appear to affect the objectivity of a research project and resolves how the conflict should be managed, reduced or eliminated. Management strategies are developed and implemented where possible to address conflicts of interest and to assure that the institution may satisfy any research obligations in an objective manner and to avoid and/or mitigate potential bias. The COI may recommend that the research may not be conducted at the University of Virginia. Resolutions adopted by the Committee are forwarded to the AVPR who then informs the investigator of the action taken by the Committee. In cases where a waiver is recommended by the Committee, the APVRGS prepares a request for a waiver for the University President's signature. Waivers may only be granted by the President of the University.

University Radiation Safety Committee (RSC)

The University has an established Radiation Safety Committee (RSC) to oversee all uses of radioactive material permitted by its licenses. This committee, through appointment of a subcommittee (HIRE-Human Investigations Involving Radiation Exposure), reviews any research that involves use of X-ray, radioisotopes or lasers. The RSC is administratively located in the Environmental Health and Safety Office (EHS) and provides expertise with regards to accepted radiation protection practices and regulations. This committee reviews any research that involves the use of X-ray, radioisotopes, or lasers. Approval by the

IRB is contingent upon approval by the RSC; however, review by the two committees may occur concurrently. The RSC is charged with ascertaining that all experimental or research uses of radioactive materials and/or ionizing radiation in or on human subjects conform to the currently accepted radiation protection regulations and practices, and the University of Virginia Radioactive Material Licenses on file with the U.S. Nuclear Regulatory Commission and the Virginia Department of Health. If RSC review is completed after the IRB review, the IRB chair reviews any RSC comments. If the chair believes the suggested changes are appropriate and qualify as minor modifications, the IRB chair reviews these through an expedited process. If changes exceed minor modifications, the IRB chair refers the application back to the full board for review. The protocol will not be opened to enrollment until IBC approval is received by the IRB-HSR.

Institutional Biosafety Committee (IBC)

The IBC is administratively located in the VPR and reviews all University research and teaching activities conducted by faculty, staff, students and/or visiting scientists on University property that involve the use of biological agents. Biological agents are defined as microorganisms, recombinant DNA experiments as defined by NIH Guidelines, materials derived from human and non-human primates, or biological toxins. Registration with the IBC is required prior to initiation of research with biological agents. If applicable, the IBC notifies the IRB of its approval of projects using biological agents, but deliberations of the IBC are not shared with the IRB unless there are specific subject protection issues raised by the IBC. IRB approval is contingent upon IBC approval when the research involves gene If IBC review is completed after the IRB review, the IRB chair reviews any IBC comments. If the chair believes the suggested changes are appropriate and qualify as minor modifications, the IRB chair reviews these through an expedited process. If changes exceed minor modifications, the IRB chair refers the application back to the full board for review. The protocol will not be opened to enrollment until IBC approval is received by the IRB-HSR.

Cancer Center Protocol and Review Committee (PRC)

The role of the PRC is to review all studies involving patients with cancer that have not received a NIH or equivalent peer review. NIH-equivalent peer reviews would include those by the American Cancer Society, Department of Defense, or National Science Foundation. In practice, the Committee reviews all studies involving patients with cancer that are sponsored by drug companies and in-house studies. The Committee does not provide a formal review of Cooperative Group protocols (COG, RTOG, ECOG, NSABP, ACOSOG, and Coalition of National Cancer Cooperative Groups) because these studies have already received an exhaustive peer review by the National Cancer Institute through its Cancer Therapy Evaluation Program (CTEP) Branch. IRB approval is contingent upon approval of the PRC.

Office of Sponsored Programs (OSP)/ School of Medicine Grants and Contracts Office

Staff of the IRB and OSP SOM Grants and Contracts Office will share contract and study information as necessary for each industry sponsored protocol to ensure that protocol, consent, and contract language are consistent with language required by 45 CFR 46.116 and 21 CFR 50.20 and .25

Privacy Office

Staff of the IRB and IRB members may consult with the University Privacy Officer on matters concerning the management of personal health information (PHI) as it relates to the enforcement of Health Insurance Portability and Accountability Act (HIPAA) of 1996 research regulations.

School of Medicine Clinical Trials Office

An approval from the School of Medicine Clinical Trials Office will be required if:

- The UVA PI is the PI for all sites in a multi-site trial
- The UVA PI is the holder of the IND or IDE (will also check need for IND/IDE)
- IND/IDE held by outside PI

The determination of whether or not an IND application is required is made by the IRB-HSR.

The School of Medicine Clinical Trials Office (SOM-CTO) staff is available to assist the investigator in contacting the FDA and writing a position statement to the IRB-HSR regarding the need for an IND.

If it is determined that an IND is required, the SOM-CTO personnel are also available to advise researchers regarding the application preparation.

In addition the IRB requires researchers to obtain SOM- CTO approval for these types of studies. The SOM-CTO review includes careful attention to the Data Safety Monitoring Plan, and Data Collection Forms. This review must take place before the IRB will allow subjects to be enrolled.

Deadline to Incorporate Pre-Review Recommendations

When a protocol is pre-reviewed, the investigator will receive correspondence detailing requests for revisions, clarification, or additional information. When the modifications are made and submitted to the IRB, they are reviewed by administrative staff and the IRB Chair, Vice Chair or member designee.

The investigator has 90 days to respond to the revisions requested. If the investigator does not respond in 90 days, the application is withdrawn and returned to the investigator. If the investigator wishes to conduct a study that has been withdrawn, the investigator must submit a new application, incorporating comments from the prior IRB review.

Please note that this procedure is in effect for ALL studies- regardless of review type.

POTENTIAL OUTCOMES OF IRB-HSR REVIEW

Potential Outcomes of Exempt or Expedited Review

When a protocol is reviewed by exempt or expedited methods, the investigator will receive correspondence detailing requests for revisions, clarification, or additional information. The **investigator has 90 days to respond to the revisions requested**. If the investigator does not respond in 90 days, the application is deactivated and returned. If the investigator wishes to conduct a study that has been deactivated, the investigator must submit a new application, incorporating comments from the prior IRB review When the modifications are made and submitted to the IRB, they are reviewed by administrative staff and the IRB Chair, Vice Chair or member designee. If there is disagreement between the IRB and the study team regarding a study- the IRB cannot disapprove a study by expedited review. The protocol would be sent to the Full IRB for review. When approved the principal investigator is sent an approval form that includes information on the date of human subject's expiration of approval. The PI is also sent any additional documents such as approved consent forms.

Potential Outcomes of Full Board Review

The IRB may come to one of five determinations regarding an application:

APPROVED: The PI will be given the original signed IRB Approval Form, the original stamped approved consent form and the original training certificate. The approval date is the date the protocol was reviewed and approved by the board. The expiration date is one year minus one day from the date the protocol was reviewed by the full board, unless the board has stipulated an earlier expiration date. At the time the study is initially approved the IRB will determine the frequency with which this review is to be done. This is normally done at least once a year, but may be required more frequently if the study involves a very new procedure or involves a considerable risk to the subject. A copy of the IRB Approval Form, the original of the stamped approved consent form and the training certificate will be filed in the protocol file in the IRB office.

APPROVED PENDING MINOR MODIFICATIONS: The investigator will receive an approval form stating conditions which need to be met in order to be able to enroll subjects in the study.

These conditions include minor changes to the consent and/or protocol and/or approvals from other committee. After the changes are made the investigator would then submit one copy of the protocol signed by the PI and two copies of the consent form. The changes should be tracked on the protocol and on one copy of the consent form. Once these documents are submitted the study does NOT need to go before the full board again. The modifications would be handled as an expedited event. The PI will be given an original of the approval for the modification- noting that the study status has changed to open to enrollment, the original stamped approved consent form and the original training certificate. The approval date is the date the full board reviewed the protocol and the expiration date is one year minus one day from the date the protocol was reviewed by the full board, unless the board has stipulated an earlier expiration date. At the time the study is initially approved the IRB will determine the frequency with which this review is to be done. This is normally done at least once a year, but may be required more frequently if the study involves a very new procedure or involves a considerable risk to the subject. A copy of the IRB Approval Forms, the original signed protocol, the original of the stamped approved consent form and the training certificate will be filed in the protocol file in the IRB office.

WITHHELD APPROVAL PENDING MAJOR MODIFICATIONS: The Principal Investigator will receive documentation outlining the general concerns. The investigator needs to address these concerns and re-submit copies of the revised protocol and consent form per full board requirements. The study will be reviewed again at a future full board meeting. In addition, the investigator may be asked to attend a future IRB meeting to answer questions. The investigator has 6 months to respond to the revisions requested. If the investigator does not respond in 6 months, the application is deactivated and returned. If the investigator wishes to conduct a study that has been deactivated, the investigator must submit a new application, incorporating comments from the prior IRB review.

REJECTED: The board may also decide to reject a protocol if it feels the study has major problems involving risk to participants or other significant concerns. The investigator may attend a future IRB meeting to defend the protocol if he/she wishes to pursue the study.

TABLED: The Principal Investigator will receive documentation outlining the general concerns. The investigator needs to address these concerns in written documentation or by attending a future IRB meeting. The investigator does not need to resubmit a revised protocol and consent. The study will be reviewed again at a future full board meeting.

Rebuttal or Appeal of IRB Decisions

If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision, and give the investigator an opportunity to respond in person and/or in writing.

Investigators may appeal an IRB decision. A principal investigator may appeal the decision by writing a letter to the IRB requesting reconsideration. At the discretion of the chair, the investigator may make such an appeal in person and/or in writing to the IRB.

An appeal of a disapproved research project must be reviewed at a full board meeting.

In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by the Vice President for Research or any other officer or agency of the University of Virginia, state government or federal government.

The IRB retains the final authority for approval of proposed research with human subjects.

RECRUITMENT OF SUBJECTS

Recruitment is the dialogue that takes place between an investigator and a potential subject prior to the initiation of the consent process. In some ways, recruitment is the introduction to the consent process. Recruitment may take the form of a flyer, a newspaper advertisement, etc., or a verbal exchange between an investigator and a potential subject. Investigators who are responsible for both the primary care of a client/patient and wish to consider enrolling the client/patient in a research project should carefully differentiate for the client/patient the alternatives and options of participation in the research without undue prejudice or pressure. Respect for potential subjects begins with recruitment procedures that ensure the voluntary participation of the subject. Potential subjects should not feel coerced into participating in research, nor must they fear the loss of some benefit to which they are otherwise entitled if they choose not to participate. A person in authority, such as a teacher recruiting students or a physician recruiting subjects, should take special precautions to ensure that a potential subject's decision to participate in research is not based on subtle pressures such as grades, monetary reward, or fear of loss of benefits, such as medical treatment.

Investigators proposing to recruit their students, employees or patients as research subjects should justify in the protocol the necessity for the inclusion of the dependent subject. In addition, the IRB will closely scrutinize the precautions in place to prevent the appearance of coercion in the recruitment of subjects. The investigator may contact the IRB for strategies for indirect recruitment.

Recruitment Tools

All recruitment materials are required to have IRB review and approval prior to implementation. Prior to use, each recruitment tool should have an approval and expiration date on the original tool. Audio and video tools may be excepted from this requirement. When recruiting subjects from another institution with an IRB, investigators are required to gain IRB approval from that institution. In institutions without an IRB, investigators are required to obtain a letter of agreement indicating the research can be conducted at the site and the agency or institution will review, abide by and comply with the procedures approved by the UVA IRB.

A recruitment tool informs potential subjects of a research activity and provides them with an opportunity to contact the researcher. A recruitment tool may include, but is not limited to, post-cards, flyers, advertisements, press releases, brochures, and postings on the Internet. The following information should be included:

- name and contact information of the clinical investigator and/or research facility (letterhead is acceptable).
- the condition under study and/or the purpose of the research.
- in summary form, the criteria that will be used to determine eligibility for the study.

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- time or other commitments required.

- the location of the research and the person or office to contact for further information.
- in drug or device studies, no claim should be made as to the superiority, safety or effectiveness of the drug or device. Proprietary names of study products may not be used.
- do not provide excessive monetary or other incentives that could be interpreted as inappropriate or coercive.
- are consistent with protocol.

Due to contractual obligations, recruitment tools should not include any proprietary identifiers, contain therapeutic or outcome claims or mention the corporate sponsor by name.

The IRB considers the following in its review of advertisements:

- that no claims are made, either explicitly or implicitly, that the drug, biologic, device or investigational intervention is safe or effective for the purposes under investigation; or that the test article is known to be equivalent or superior to any other drug, biologic or device.
- that the advertising does not use terms such as “new therapy”, "new treatment", "new medication" or "new drug" without explaining that the test article or intervention is investigational; a phrase such as "receive new treatments" leads study subjects to believe that they will be receiving newly improved products of proven worth.
- that advertisements do not advertise "free medical treatment" when the intent is only to say that subject will not be charged for taking part in the investigation.
- placebo-controlled studies: the advertisements do not lead perspective subjects to believe that everyone who enrolls in the study will receive the investigational treatment.
- studies with multiple intervention arms, that subjects will be assigned randomly (or by another appropriate method) to one of the interventions (or standard, or no intervention if trial is the approved study design
- that advertisements do not emphasize the payment to subjects, if any, by such means as large or bold type.
- When advertisements are taped for broadcast, the IRB may review and approve the wording of the advertisement prior to taping and will review the final audio/video tape when completed.

For additional information see Advertising Recruitment of Children

The ethical requirement of respect for persons, as outlined in the Belmont Report, applies to children as well as adults. Children, however, are in a dependent relationship to adults and easily manipulated in an academic or clinical setting. A child’s dependent relationship entitles them to extra protections and are thus considered a “vulnerable subject population”. Investigators should take every precaution to insure that a child’s decision to participate in research is both voluntary and free from coercion. A child’s refusal to participate should not be met with a negative response or punishment.

The IRB strongly recommends that investigators address the following when submitting applications that include the recruitment of children:

- Investigators should acknowledge and create a mechanism for addressing and minimizing the coercion implicit in requests to participate from parents, teachers, or other adult authorities.
- Investigators should make provisions to minimize the fear of ridicule, social pressure, or peer pressure to participate.

- Incentives or rewards for participation may be used but should not be so valuable, within the value system of the parent or the child, as to sway the child's legitimate reluctance to participate.

Permission of the School

School officials and/or teachers do not have the authority to give consent for the participation of children in research. Only a parent or guardian may allow a child, with the child's assent, to participate in research. The IRB requires submission of proof of approval of the school district prior to allowing investigators to contact, recruit, or enroll children into a study. Investigators should contact school district officials regarding the appropriate procedures for obtaining permission to conduct the research in individual schools.

The No Child Left Behind Act of 2001(Public Law 107-110) amended the Protection of Pupil Rights Amendment (PPRA), which concerns surveys of students, in two ways:

- First, it added an eighth category to the categories of protected information in surveys of children that were already covered by PPRA.
- Second, it gave parents new rights with regard to the surveying of students who are children, the collection, disclosure, or use of information from students for marketing purposes, and certain non-emergency medical examinations.

PPRA, as amended, has two sets of requirements for surveys:

- Requirements that apply to "protected information" surveys that are funded in whole or in part by the U.S. Department of Education.
- Requirements that apply to "protected information" surveys that are funded by sources other than the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any Department of Education program (i.e. public elementary and secondary schools and some private schools).

PPRA lists 8 categories of protected information for survey responses:

1. political affiliations of student or student's parent;
2. mental or psychological problems of student or student's family;
3. sex behavior or attitudes;
4. illegal, anti-social, self-incriminating or demeaning behavior;
5. critical appraisals of others with whom students have close family relationships;
6. legally recognized privileged or analogous relationships;
7. religious practices, affiliations or beliefs of student or student's parent;
8. income.

PPRA has implications for IRBs in applying the Common Rule criteria for waiving informed consent (in section 116(d) of the Common Rule). Specifically the second IRB criterion: "research does not adversely affect the rights and welfare of subjects" is impacted because of the "rights" that PPRA gives parents.

Practical Implications in Applying the Common Rule Waiver Requirement pertaining to rights and welfare:

First Set of Requirements: US Department of Education Funded Protected Information Surveys

1. Does the research involve "protected information" surveys?

2. Are the surveys U.S. Department of Education- funded in whole or part?
3. Are the surveys "required"?

If the answer is yes to the three questions, PPRA affords parents the right to provide written informed consent.

Payment for Recruitment

Finder's fees and other financial incentives paid by a sponsor or by an investigator to others related to the recruitment of research subjects are prohibited.

No one may receive any incentive for the purpose of encouraging individuals to participate in research.

All payment by sponsors for research conducted under the auspices of the University of Virginia must be made directly to the University of Virginia and will be managed by the University.

Payments should never go directly to investigators, key personnel or subjects without first going through the University.

Payment for Subject Participation in Research

The nature, amount, and method of payment or other remuneration should not constitute undue inducement to participate (i.e., the payment should not serve as sufficient inducement for the subject to volunteer).

The IRB will consider the impact participation poses on the daily life of the potential subject. For example, the IRB will consider compensation of subjects for inconvenience posed by the research, such as:

- the time required to participate;
- travel involved and/or parking costs;
- lost time from work,
- babysitters, etc.

Investigators should include provisions in the protocol for addressing these concerns, especially for research that poses little or no direct benefit for the subjects.

Special precautions should be taken when payment is offered to a third party for the participation of someone else in the research. The IRB is concerned that such payments may constitute undue influence from the third party to the actual research participant. For example, a parent may be offered remuneration for volunteering their child to participate in a research project. In these cases, precautions should be taken to clearly separate the payment to the third party from the consent/assent process with the actual research participant. Final approval for participation rests solely with the research participant and their consent/assent takes precedence over that of the person to whom payment is offered.

Payment to research participants for participation in studies is not considered a benefit. Rather, it should be considered **compensation for time and inconvenience** or a recruitment incentive. The amount and schedule of all payments should be described in the IRB protocol at the time of initial review, including a summary of both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.

Timing of Payments

Since subjects reserve the right to withdraw their participation from the research without prejudice, payment to subjects should be prorated, i.e., partial participation in a research activity would obligate partial payment. The IRB will review both the amount of the payment, to which it is offered, and the proposed method of

disbursement to ensure that payment for participation does not constitute coercion or undue influence. Investigators should explain the payment schedule in the informed consent document.

Credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be paid at the time the study would have been completed had they not withdrawn. For example, in a study lasting only a few days, it would be permissible to allow a single payment date at the end of the study, even to participants who withdraw before completion. However, for a study lasting several months, it would not be permissible to allow a single payment date. Participants who withdraw before completion of the study should receive accrued compensation in a timely manner.

Completion Bonus

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion is acceptable, providing that such incentive is not coercive. The IRB will determine whether the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

Disclosure of Payments

All information concerning payment, including the amount and schedule of payment(s), should be described in the informed consent document.

Alterations in Payments

Any changes in participant compensation or flexibility of the payment schedule must be reported to the IRB as a modification prior to implementation.

Difference Between Compensation and Reimbursement:

Reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Compensation is "payment" for things such as time, discomfort, inconvenience.

Requirements for reimbursement:

Reimbursements must be paid with Oracle Expenditure types found under the Travel Heading. For instructions on how to process a reimbursement please see "Goods and Services Procurement Guide". You may also call the Procurement Help Desk at 924-4212. The money will not be reportable to the IRS as income, but will be withheld if the subject owes money to the state. You may want to speak to procurement regarding the typically turn around time for reimbursements, so that you are including accurate information in the consent form. Another option for reimbursements is a petty cash fund. Speak with Procurement regarding this option. Please do not state in the consent form that you are "reimbursing" the subject if you do not plan to process the payment under the expenditure type found under the Travel Heading- since the tax ramifications are different.

Requirements for compensation:

Compensation may be given in several different forms. These may include check via oracle, gift cards, petty cash or small gifts such as pencils/ stickers. The state encourages the use of check via oracle for most payments. However circumstances do allow other methods of compensation in special circumstances if approved by the IRB. If using oracle the expenditure type of Services, Human Subject Payments found under Contractual Services should be used. Please note that the paid amount will be reportable to the IRS as income and will be

withheld if the subject owes money to the state. It is critical that the researcher does not imply in the consent form that one is being "reimbursed" if you plan to process the payment via compensation methods, since there are very different tax implications for the subject.

MANAGING A PROTOCOL AFTER INITIAL APPROVAL

Modifications (Amendments/ Revisions) to Currently Approved Research

The terminology used to describe a change to a protocol may vary, including terms such as modification, amendment or revision. Typically outside sponsors may call any change to the protocol an amendment. For purposes of this document the term modification will be used to designate a change.

All modifications to currently approved research are required to have IRB review and approval prior to implementation except when necessary to eliminate apparent immediate hazards to the subject.

The modification application should include any required changes to the protocol, consent or other study documentation. The modification reviewer has access to the same documentation as the initial or continuing reviewer and is expected to conduct the review with the same diligence as an original or continuing review regardless of whether or not the review is expedited or full board review.

Regulations permit the use of expedited procedures for review of minor changes to previously approved research during the period for which the approval is authorized. Modifications that alter the risk/benefit ratio are assigned to a primary reviewer and presented to the full board at a convened meeting.

The essence of the study should be summarized by the reviewer for IRB members and the reviewer should state what the proposed modification is and how it will affect the conduct of the study, the risk/benefit ratio, and whether or not the modification should be approved as written. If the modification requires a change in the informed consent document, then the reviewer must review that change and recommend appropriate board action. Modifications submitted to the IRB, along with supporting correspondence, are entered into the IRB database, and placed in the study file.

Investigators are notified in writing of the decision of the IRB and of any changes required. Modification approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent a modification approval form. The IRB may only approve modifications through the current approval expiration period, unless considered at the time of continuation review. Upon receipt of the approval for the modification, the investigator may initiate the modification.

If approved research is changed to eliminate an apparent immediate hazard(s) to the subject, the investigator is required to notify the IRB of the change(s) promptly (within five (5) business days). The IRB will review at the next convened meeting to determine if the change(s) instituted were consistent with the subject's continued welfare.

Submission of Materials and Feedback Time Frame

Approval of a modification does not extend or otherwise change the project's expiration date.

Deadlines for submissions only apply to full board reviews. Refer to the Meeting Dates schedule on the IRB website. Full board reviews must be submitted by a deadline that is usually 7 days prior to the convened meeting.

Expedited modifications can be reviewed at anytime and will be, typically, reviewed within 3-5 business days after which the researcher will receive feedback from the review.

Continuing Review Process

Establishing Continuing Review Parameters for Approved Protocols

- Except for studies determined to be exempt from IRB oversight, all human subject's studies are required to undergo continuing review based on the level of risk as assessed by the IRB. This review takes place no less than annually, and may require more frequent review or reports as determined by the IRB. For projects receiving full board review, the length of approval is calculated from the date of the full board review. When a primary reviewer has been assigned, that reviewer is asked to provide a recommendation for the length of approval. The appropriate length of approval is considered as a part of the full board discussion.
- Continuing review of expedited or full board approved research will be conducted with the same diligence as utilized with the initial review of the research. The review should be substantial and complete. Reviewers have access to the original submission, all documents submitted since the beginning of the research and any new documentation submitted with the continuing review application.
- For projects approved via the expedited process, the chair, vice chair or experienced member designee conducts the review and determines the length of approval but, the approval time is still no greater than annual.
- Continuations may be reviewed by expedited review when:
    - No subjects have enrolled OR
    - the research is permanently closed to the enrollment of new subjects AND
    - all subjects have completed all research-related interventions,
- Continuing IRB review is required as long as the research remains active even if only for long-term follow-up of subjects.

Projects requiring review more frequently than annually may include:

- Experimental therapies in which the clear potential for significant adverse experiences have been identified at the time of review;
- Non-therapeutic projects based on risk information provided at the time of initial review;
- Projects in which new information provided during the duration of the study (including at the time of continuing review) indicates a high probability of significant adverse experiences not previously reported; or
- Projects in which local or outside adverse experience reports create new concerns regarding the need for closer project scrutiny.

In such cases, approvals may be granted for time periods less than one year or, as may be more appropriate, for a limited number of subjects over a period not to exceed one year.

Projects requiring verification of changes from a source other than the PI

Criteria that the IRB may consider when making this determination include:

- Studies involving an investigator-held IND or IDE
- Studies with a conflict of interest

- Investigators with previous non-compliance, substantiated complaints or allegations of non-compliance
- Investigators who have had previous for-cause FDA or other for cause internal or external regulatory audits
- Studies involving high-profile topics or methodologies (gene transfer, embryonic stem cells)
- Studies involving higher-than-average risk (phase 1 clinical trials)

When the IRB-HSR determines that such verification is required, it should establish the sources it will use. These sources include, but are not limited to those listed below.

- VPR Post Approval Monitors
- School of Medicine Clinical Trials Office
- General Clinical Research Center
- Investigational Pharmacists
- Sponsors
- External regulatory agencies (OHRP, FDA)
- Research Subjects
- General Counsel
- Conflict of Interest Committee
- University officials who oversee research with humans such as Research Deans or department chairs;
- Other UVA compliance committees

Submission for Continuation Review (Protocol Status Reports)

- Approximately eight weeks before the scheduled Meeting Date, the IRB staff will send out the Status Report Forms for those protocols approved via expedited or full board review along with the appropriate email to the Principal Investigator (PI), Study Coordinator (if designated), the Department Contact (if designated) Faculty Advisor (if designated) and the IRB Departmental Coordinator (if designated). If the PI does not have an e-mail address, a hard copy of the status report will be printed out and sent through UVA messenger mail to the PI only. The Status Report will have the due date (approximately one month prior to the meeting date) listed on the form.
- If the approval expires prior to submission of the continuation application, the investigator is required to suspend subject contact and data collection until the continuation is approved by the IRB. For therapeutic studies where subject safety is a concern, federal regulations allow some flexibility towards the continued treatment for currently enrolled subjects. However, no new subjects may be contacted, recruited, or enrolled in the study until the investigator obtains current IRB approval.
- If the PI does NOT return the completed Status Form by the Late Due Date the PI will be sent a letter notifying him that the protocol has expired. A copy of this letter will go to the Department Chair, the appropriate grants office and others as indicated. In addition the IRB Chair, vice-chair or designee may refer this PI to the School of Medicine Clinical Trials Office for a Post Approval Monitoring (PAM) review. In addition, the event of "Closed by PI" with a comment of "expired" will be entered in IRB Online.
- When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported to the Office of Human Research Protections (OHRP) as a suspension of IRB approval under HHS regulations.

- If the PI wishes to reopen the protocol the PI will need to update the protocol and consent (if plan to reopen to enrollment) to the current template. If the protocol does not meet exempt or expedited criteria it will need to go to the full board for approval. In addition, the IRB staff will notify the PAM auditors by email. PAM will initiate audit procedures.
- If a study is more than five years old and still enrolling, the PI will be notified that the protocol and consent form(s) will need to be updated to the current template using IRB online.
- Once completed continuing review materials are received, a determination is made whether the continuing review is eligible for expedited review or if it should be scheduled for full-board review.
- Continuing review of expedited or full board approved research will be conducted with the same diligence as utilized with the initial review of the research. The review should be substantial and complete. Reviewers have access to the original submission, all documents submitted since the beginning of the research and any new documentation submitted with the continuing review application. This substantial review is designed to ensure that the rights and welfare of subjects continue to be protected.

  Reviewers are asked to review the status report and supporting documents, including the revised protocol and informed consent document, to ensure compliance with current regulations and standards. Reviewers should:

  - Consider if new or additional risks have been identified (e.g. number of serious adverse reactions, review DSMB reports, if available) which would require changes to the protocol, consent form, review frequency, etc.
  - Identify protocols that should be suspended or terminated because research is not being conducted in accordance with IRB requirements.

  In conducting a review, members should ensure that the same standards as applied in the original review are still valid (e.g. minimize risk, risks reasonable in relation to anticipate benefits, equitable selection, adequate informed consent process and documents, monitoring data (DSMB reports, etc.) to ensure subject safety, privacy protections, and appropriate safeguards for vulnerable populations).
- Investigators are notified in writing of the decision of the IRB and any changes required. Continued approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent documentation indicating the date of the next study expiration.

Unanticipated Problems

An unanticipated problem is any event, experience, issue, instance, problem, or outcome that **meets all 3 of the following criteria:**

- Unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol –related documents AND the characteristics of the subject population being studied.
- Related or possibly related to participation in the research. This means that there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research study

- The event, experience, issue, instance, problem or outcome suggests that the research places the subject or others at greater risk of harm that was previously known or recognized OR results in the subject or others actually incurring harm
- ALL Unanticipated Problems must be reported to the IRB

Adverse Event Reporting-

There are many definitions for and adverse event. One example is:

Adverse events are untoward or undesirable experiences associated with research, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events may be the result of:

- the interventions and interactions used in the research,
- the collection of identifiable private information in the research,
- an underlying disease, disorder, or condition of the subject, and/or
- other circumstances unrelated to the research.

Aggregate Review of Research Data

The Data and Safety Monitoring Plan (DSMP) template produced using Protocol Builder when a study presents greater than minimal risk to subjects, asks the Principal Investigator (PI) to determine the appropriate frequency and appropriate content for aggregate reviews.

Responses to these template questions can differ widely depending on the type of risks, and the vulnerability of the study population. It can be frustrating for the study team to determine what answers best suit the type of risk the study presents to their subjects. In addition, it is important to note that the responses to these questions must be as accurate as possible since Post Approval Monitors (PAM) will be looking for documentation that aggregate reviews are performed exactly as described in the DSMP. Therefore the PI will want to be sure to select the appropriate frequency and content in the DSMP.

What is an aggregate review?:
Aggregate Review is the cumulative review of specific data that might impact the safety and risk/benefit analysis for a study.

Who is responsible for the aggregate reviews?
If there is not another person or body assessing safety of a study on an ongoing basis (medical monitor, DSMB, etc.) then the responsibility for completing these reviews falls to the PI. If the study has a Data and Safety Monitoring Board the UVa PI will likely NOT be responsible for aggregate reviews. In this case it is likely that the DSMP should not have the PI checked as the only person overseeing aggregate safety for the study- because the DSMB is responsible for that function.

Determining the frequency of aggregate review?

For studies that are deemed greater than minimal risk (require full board review), there is a question in the Data and Safety Monitoring Plan template about the aggregate review. The question reads as follows:

> Answer this question ONLY if the PI is the ONLY person responsible for overseeing the safety of the study.
>
> How often will aggregate review occur?

The decision regarding the frequency of PI aggregate review must be based on the amount of risk to which subjects are exposed, the likelihood that previously unknown adverse effects might be discovered, and the vulnerability of the population under study. Again, if the study has a Data and Safety Monitoring Board the UVa PI will likely NOT be responsible for aggregate reviews. In this case it is likely that the DSMP should not have the PI checked as the only person overseeing aggregate safety for the study- because the DSMB is responsible for that function.

<u>Recommendations for Annual Aggregate Review:</u>
For studies that are deemed just slightly greater than minimal risk, an annual review is fine. These studies require full board, but present only slightly greater than minimal risk to the subjects. Examples of these kinds of studies include:

- Well-described, short term treatments to relieve common symptoms with known safety data at a single site,
- Trials with procedures such as indwelling catheters, endoscopy, lumbar puncture, bone marrow biopsy, oral glucose tolerance, induced sputum, skin biopsy, and routine imaging studies. These studies are commonly done in clinical practice. The risk profile for these procedures is well understood. Annual review would be sufficient even if these tests are being done solely for research.
- Collection of sensitive information via questionnaire or survey where a privacy plan is in place.
- Therapeutic trials of an agent or device that are already approved for use in the study population to be studied, for the indication under study, at the dose, and frequency which is already approved and the study is taking place at a single site (UVa Only)
- Blood draw studies where the volume and/or frequency exceeds that which is allowed under expedited criteria.

<u>Recommendations for Monthly Aggregate Review:</u>
For studies that pose significant risk to the subject, a monthly aggregate review would be appropriate.
Some examples of these kinds of studies include:

- Clinical trials of diseases where the endpoints are major morbidity or mortality
- Study involves the assessment of serious toxicity,
- Studies requiring the implantation of any device solely for research
- Studies on new chemicals, drugs, or biologics for which there is limited or no available safety data in humans
- Gene transfer studies
- Multisite studies involving risk to subjects
- Studies involving high-risk clinical procedures performed solely for research purposes

<u>Recommendations for Aggregate Review performed at Frequencies other than Annual or Monthly:</u>
For studies that do not fall neatly into "slightly greater than minimal risk" or "significant risk", an alternate timing for aggregate review (every other month, quarterly, every 6 months, etc) may be appropriate. These kinds of studies may present moderate risk to subjects and include the following:

- Interventions performed for research that present low or minimal risk to subjects and subjects represent a vulnerable population (children, prisoners, etc.)
- Subjects with diseases are exposed to placebo,
- Therapeutic interventions involving procedures such as insulin clamps or organ biopsies
- Studies that involve subjects with illness being treated with procedures that may result in moderate to severe adverse events
- Studies involving combinations of previously approved therapies for a particular condition (approved for the population under study and the approved dose, for the approved indication at the approved frequency, using the approved route.)

Determining the appropriate content for aggregate review:

The DSMP template asks the PI to check what items will be reviewed at the time of aggregate review.

- If the study team is not collecting the data, do not indicate that data will be examined in the aggregate review! For example if there are no dose escalation rules, de-escalation rule, study stopping rules, etc., then do not indicate that these data will be reviewed during aggregate review. This may seem obvious, but it is one of the most frequent errors found during DSMP review.
- It is impossible to review for safety if adverse events and unanticipated problems are not reviewed. It is almost always safe to assess these criteria during aggregate review.
- Check only the criteria for which the study team has access.
- Check only the criteria that make sense for the study. For example, if the study involves a one-time questionnaire, then assessing early withdrawal data will likely not be helpful and does not make sense for a study of this nature.
- Be clear in the DSMP what criteria will be reviewed and at what frequency. Perhaps the study team plans do a monthly review of AEs but only wish to review Early Withdrawal data on an annual basis. Make sure it is clearly documented in the DSMP what criteria the study team plans to review and how often it is intended to be reviewed.

How do you do an aggregate review?

1. At the frequency noted in the DSMP for the protocol, the PI will pull the cumulative information collected thus far for the data points indicated per the DSMP (e.g. AEs, Unanticipated problems etc.). The data may be found in individual case files, in a spreadsheet or in a database from which reports can be generated. How this data is stored and pulled together or generated for aggregate review must be determined by the study team early in the study.
2. The PI will review all of the data asking the following questions:
   - Are there any trends noted?(safety, enrollment, early withdrawal, etc)?
   - Does the risk/benefit profile remain as previously described in the protocol?
   - Are there any modifications to the protocol and consent that would diminish additional risks, promote enrollment, encourage subjects to complete the study etc.
3. The PI needs to make the following decisions based on the aggregate review:
   - Is it safe for this study to continue as is; or is a modification required OR must the study be closed?

How do you document the aggregate review?

If only annual aggregate reviews are required, a provision is made to document annual aggregate reviews in the Protocol Status Form which is e-mailed out to study teams prior to Continuation review. If this section of the Protocol Status Form is completed, then no further documentation of an annual review is required.

If the aggregate review must take place at a frequency other than annually, then documentation for the aggregate review should include the following:

- IRB-HSR Number
- Protocol title
- Date of the review
- Content of the review (AEs, etc.)
- Determination of continuation status (study to continue with no modification required due to this review, study to continue with the following modifications: *insert*, or study to be stopped due to (insert).

The Aggregate Review Form is available to assist in documenting the aggregate review. This form or something similar to this form may be used for documentation purposes.

What documentation must be sent to the IRB-HSR?
There is a question in the DSMP that asks how often documentation of aggregate review will be submitted to the IRB. If it has been determined that an annual submission is sufficient, then the researcher need only complete the Protocol Status Form that is sent for the Continuation review. No additional documentation needs to be submitted.

If some other frequency has been checked, submit documentation of aggregate reviews to the IRB at the frequency indicated in the DSMP. The Aggregate Review Form may be used for this purpose.

What must be maintained in the Study Records/Regulatory Files:
Make sure the documentation of the aggregate reviews is safety stored. This documentation will be reviewed during Post-Approval Monitoring.

Protocol Violations and Enrollment Exceptions

Investigators are responsible for conducting human-subjects research in accordance with all applicable federal and state regulations, UVA IRB policies and procedures..

The federal regulations specifically require the IRB to review proposed changes in a research activity, and to ensure that such changes in approved research are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45CFR46.103(b)(4)(iii) and 21CFR56.108(a)(4)]. Research activity includes all aspects of the conduct of the research study, e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc. - all of the information outlined in the protocol submission and reviewed and approved by the IRB. Noncompliance with these regulations, UVA IRB policies and procedures, or UVA IRB requirements during the conduct of a research study results in a protocol violation, and as such must be reported to the IRB.

Protocol Violations

A protocol violation is any unapproved change, deviation, or departure from the study design that NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. These protocol violations may be major or minor violations.
These protocol violations may be major or minor violations. You can review a summary of minor and major violations that are reportable to the IRB on the Protocol Violation and Enrollment Exception Reporting Form.

Enrollment Exceptions:

- Definition: Enrollment of a research subject that fails to meet current IRB-HSR approved protocol inclusion criteria, or falls under protocol exclusion criteria.
- Enrollment exceptions only apply to a single individual. Such a request should be rare and justified in terms of serving the best interests of the potential study participant

Maintenance of Informed Consent Documentation

Principal Investigators are responsible for maintaining original copies of consent/authorization forms signed by subjects, in a secure location, for at least six (6) years following completion of the research and longer, if required by the funding source or sponsor. A copy of an informed consent document for particular treatments or procedures shall be placed in the subject's medical record in accordance with Virginia state and local government regulations.

In cases where Principal Investigators transfer their research programs to other institutions, the disposition of consent/authorization forms must be discussed with the IRB administrative staff.

Miscellaneous Reporting to the IRB by an Investigator

Unexpected pregnancies of subjects that might affect the safety of the mother or fetus, incarceration of subjects (a person incarcerated after consenting to be a research subject is seldom allowed to continue as a research subject) not previously incarcerated, and results of Data and Safety Monitoring Boards will be reported to the IRB as soon as the investigator is aware of the occurrence. The IRB will assess this information and provide guidance as to whether or not the subject may remain in the study or if changes will be required in the research because of new safety information from the DSMB. Senior IRB members will be available to consult with investigators about these or any unusual problems that may occur concerning research.

Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of human subject's research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected, related and serious harm to subjects. Any suspension or termination of approval includes a statement of the reasons for the IRB's action and is reported promptly to the investigator, the investigator's department chair, and to Office of Sponsored Programs/ Office of Grants and Contracts, . The IRB may require remedial action or education as deemed necessary for the investigator or any other key personnel. Federal regulatory agencies are notified as required by federal regulation.

Suspension is the temporary closing of a human research project or discontinuing an investigator's privilege to conduct human subject research. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the research may proceed. The IRB will make this determination.

Termination is the ending of all activities related to a human research project or an investigator's privilege of conducting human subject research at the University of Virginia except for the continuation of follow-up activities necessary to protect subject safety.

Reporting to Federal Oversight Agencies

The IRB chair notifies institutional officials, and they together notify OHRP (in accordance with the terms of the University of Virginia FWA) and the FDA (for projects subject to 21 CFR Parts 50 and 56), and the funding source in a timely manner of any:

- serious or continuing non-compliance;
- unanticipated problems involving risks to subjects or others; or
- suspension or termination of IRB approval for a project. Any suspension or termination of approval will include a statement of the reasons for the IRB's action.

UVa Institutional Officials are copied on all correspondence to Federal oversight agencies.

In addition the IRB must notify OHRP of changes in IRB Membership.

Reporting and Notification to FDA, OHRP, IRB, and Subjects

Reporting the progress of the research project and incidence of injuries to human subjects is a required, essential component of the institutional approval process. The scope and frequency of reporting will vary among projects. Varying reporting requirements may be based on the degree of risk to the human subjects involved in the study, the amount of prior knowledge or experience regarding the use of human subjects in the investigation, the level of experience of the professional personnel, and the potential liability to UVA.

Protocol Closure

Principal investigators have the responsibility of informing the IRB when a protocol has been completed.

A protocol is considered to be open and active until the investigator has submitted a Closure Form to the IRB.

Investigators will be notified by the IRB at least annually following the initial approval of the protocol. At these notification intervals, investigators are to submit either a continuation request or a Closure Form.

Faculty advisors for student research have the obligation to ensure that the Closure Form is filed with the IRB in a timely fashion.

When a principal investigator terminates employment or other association with UVA, he or she is obligated to submit a Closure Form to the IRB or formally transfer the protocol to another principal investigator via a modification which is reviewed and approved by the IRB. In very rare cases, the IRB may grant special permission for the departing individual to remain as principal investigator on the project. Cases are reviewed on a case by case basis.

A protocol may be closed when **all** of the following apply:

- All subject recruitment and enrollment is complete (i.e., no new subject recruitment or enrollment are ongoing)
- All subject specimens, records, data have been obtained (i.e., no further collection of data/information from or about living individuals will be obtained)

- No further contact with subjects is necessary (i.e., all interactions or interventions are complete and no further contact with enrolled subjects is necessary)
- Analysis of subject identifiable data, records, specimens are complete (i.e., use or access to subject identifiable data is no longer necessary. **Note: this includes review of source documents by study sponsors.**

GLOSSARY/ACRONYMS

IRB-HSR Glossary/Acronyms

FORMS

IRB-HSR Forms

USEFUL WEBSITES

IRB-HSR Useful Websites

FREQUENTLY ASKED QUESTIONS

IRB-HSR FAQ

FEEDBACK TO THE IRB-HSR

Provide Feedback

ETHICAL PRINCIPLES

REGULATIONS/ GUIDANCE